

European Association of Urology Guidelines

2017 edition

European Association of Urology Guidelines 2017

Introduction

We are honoured to present the 2017 edition of the European Association of Urology (EAU) Guidelines. The EAU Guidelines are the most comprehensive continuously updated guidelines, available for urologists and related specialities, produced by a dedicated Guidelines Office involving approximately 300 international experts. The EAU guidelines are recognised worldwide as an important resource to assist clinicians in their everyday practice, they are currently available in more than 30 languages and endorsed by more than 55 national and scientific societies throughout Europe and the world. Furthermore, this year we are delighted to announce the inclusion of two new topics, Renal Transplantation and Thromboprophylaxis.

Clinical practice guidelines not only play a pivotal role in health care practice, but are also a vital resource for the advancement of medical education. The EAU Guidelines Office are committed to actively pursuing effective collaborations both within the EAU and externally which help to further the medical education of young clinicians. A key example of this is the EAU Guidelines Office systematic review programme, the success of which is measurable in the numerous European Urology publications it has produced to date. In this endeavour the EAU Guidelines Office is exceptionally grateful for the continued support and active collaboration of Prof. Dr. J. Catto editor-in-chief of European Urology. Other highly productive collaborations include the hosting of multiple European School of Urology courses on changes in the guidelines and evidence-based medicine methodology for which the continued support of Prof. Dr. J. Palou has been invaluable. In the coming year we will continue to build upon and grow these collaborations.

Adherence to national and international clinical guidelines is sub-optimal throughout Europe therefore, the development of clinical guidelines must fundamentally be supported by an effective dissemination and implementation strategy. Dissemination should be an active process in which tailor-made information is actively imparted to the appropriate audience/users. Effective implementation of clinical guidelines involves the identification of barriers to knowledge transfer, or more importantly, the identification of the optimum interventions to limit or overcome such barriers. During the course of 2017 both the EAU Guidelines Social Media (SoMe) and IMPact Assessment of Guidelines Implementation and Education (IMAGINE) groups will continue to actively drive these processes forward, allowing for the continued optimisation of urological healthcare resources ultimately, focused on improving patient outcomes.

Moving forward, as of 2018, the EAU Guidelines will begin to adopt a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to measure the quality of evidence of studies included in the guidelines and to grade guidelines recommendations. The strength of each recommendation will be determined by the balance between desirable and undesirable consequences of alternative interventions, the quality of evidence for each intervention as well as the nature and variability of patients' values and preferences. The strength of each recommendation will be represented by the words 'strong' or 'weak'. The panels will provide both 'strong' and 'weak' recommendations 'for' or 'against' each intervention. This system will be introduced across all EAU Guidelines, in a staged process, the aim being to provide transparency between the underlying evidence and a given recommendation.

The yearly publication of the EAU Guidelines would not be possible without the unwavering support of the EAU Executive Committee and Management team, our highly valued Guidelines Panels and young Guidelines Associates, our EAU membership and every user of the Guidelines globally. So, on behalf of the EAU Guidelines Office Board, thank you for your support and inspiration.

We hope you enjoy using the 2017 update of the EAU Guidelines!



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Methodology section

Clinical guidelines development is one of the core activities of the European Association of Urology (EAU), with the 2017 Guidelines covering the majority of the urological field. The EAU clinical guidelines, which are updated based on systematic reviews of the available clinical evidence, are developed to support clinicians in making informed decisions in their care of patients.

The Guidelines Office (GO), consisting of more than 300 clinicians, is responsible for the production of these documents. Their efforts are supported by a number of expert Committees, each with specific tasks and responsibilities.

The EAU GO unified production methodology aims to:

- ensure scientific quality, accuracy and currency of information;
- promote a sustained quality improvement;
- contribute to the dissemination and implementation of all EAU Guidelines publications.

Systematic Review development

The EAU GO have set up a management structure to support development of systematic reviews (SR) involving young clinicians (Guidelines Associates) who are supported by methodologists and statisticians. These SRs are based on clinical questions prioritised by the Guideline Panel responsible for each topic and their findings are incorporated into the EAU guidelines as they become available. Benefits and harms of interventions are addressed in detail, both in the development stage of the clinical question and when review findings are being incorporated and treatment recommendations formulated. Whenever possible, patient input is sought at both the development stage of the SR questions as well as when guidelines recommendations are being drafted. Patient organisations are invited to take part in review of the EAU Guidelines documents prior to publication. This is a rolling programme, with the ambition to address the majority of key clinical questions covered by the EAU guidelines.

All SRs are performed using standard Cochrane SR methodology: (<http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>). Two independent reviewers screen abstracts and full texts, carry out data abstraction, assess risk of bias and do a GRADING exercise [1-4]. The results are presented in tables showing baseline characteristics and summaries of findings. Meta-analyses are performed only as part of a SR when several randomised controlled trials have addressed the same question and outcomes are reported homogeneously. For lower level data, narrative syntheses of the evidence are provided. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance is followed [5].

Independently of these SRs, each Guideline Panel has undertaken a separate systematic search, tailored to their individual guideline. These are broad searches (Scope/Horizon searches) which are developed to:

- ensure that the available clinical evidence is identified in a structured unbiased fashion;
- ensure that significant data are not missed;
- inform on the need to update guidelines documents;
- identify gaps in the literature and prioritise future systematic review activities.

The results of these searches are selected and assessed in a structured fashion by Guideline Associates and Guideline Panel members, although no detailed evidence summaries are produced. The search histories are available online in the Appendices and Publications sections of each guideline topic (www.uroweb.org/guidelines/).

Level of evidence and grading systems

Modified Oxford Centre for Evidence-Based Medicine Levels of Evidence approach

The majority of recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [6].

Table 1: Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

* Modified from [6].

Modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

Moving forward, the EAU GO have adopted a modified GRADE approach to assess the quality of evidence of studies included in the guidelines and to grade guidelines recommendations [7-9]. Assessment of the evidence using GRADE methodology has been the standard for all new systematic reviews undertaken by the GO in the past two years. GRADE methodology will now be introduced across all EAU Guidelines documents, in a staged process, which will be completed by 2018.

To allow for a transparent assessment of how recommendation statements have been developed, a Summary of Evidence (SOE) table will be provided for each recommendation within the guidelines which will address a number of key elements:

1. The overall quality of the evidence which exists for the recommendation;
2. The magnitude of the effect (individual or combined effects);
3. The certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. The balance between desirable and undesirable outcomes;
5. The impact of patient values and preferences on the intervention;
6. The certainty of those patient values and preferences.

These key elements in the SOE tables are the basis which panels use to define the strength of each recommendation. The strength of each recommendation will no longer be represented by alphabetic characters, but rather by the words 'strong' or 'weak' [9]. The panels will provide both 'strong' and 'weak' recommendations 'for' or 'against' recommending an action based on the information found in the SOE tables. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

References

1. Atkins, D., *et al.* Grading quality of evidence and strength of recommendations. *BMJ*, 2004. 328: 1490.
2. Guyatt, G., *et al.* Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest*, 2006. 129: 174.
3. Guyatt, G.H., *et al.* What is "quality of evidence" and why is it important to clinicians? *BMJ*, 2008. 336: 995.
4. Guyatt, G.H., *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 2008. 336: 924.
5. Moher, D., *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*, 2009. 62: 1006.

6. Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
7. Guyatt, G.H., *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 2008. 336: 924
8. Guyatt, G.H., *et al.* What is "quality of evidence" and why is it important to clinicians? *BMJ*, 2008. 336: 995
9. Guyatt, G.H., *et al.* Going from evidence to recommendations. *BMJ*, 2008. 336: 1049.

The assistance and support of National Urological Associations has been invaluable for the European Association of Urology guidelines project over the past years. Whilst in many European countries the EAU guidelines are being used in clinical practice, or form the basis of national urological guidelines, the EAU Guidelines Office have only recently started to formalise endorsement of their guidelines. Formal replies have been sent in by the following National Urological Associations within Europe and beyond:

National Societies Endorsements

The Algerian Association of Urology	The Italian Association of Urology
The Argentinian Society of Urology	The Kosova Urological Association
The Armenian Association of Urology	The Latvian Association of Urology
The Urological Society of Australia and New Zealand	The Lithuanian Urological Society
The Austrian Urological Society	The Luxembourg Society of Urology
The Belarusian Association of Urology	The Macedonian Association of Urology
Belgische Vereniging Urologie	The Malaysian Urological Association
The British Association of Urological Surgeons	The Maltese Association of Urology
Brazilian Urological Association	The Mexican Society of Urologists (SMU)
The Bulgarian Association of Urology	Norwegian Urological Association
La Sociedad Chilena de Urología	The Polish Urological Association
The Chinese Urological Association	The Portuguese Urological Association
La Sociedad Colombiana de Urología	The Russian Society of Urology
The Croatian Society of Urology	The Romanian Association of Urology
The Cyprus Urological Association	Société Belge d'Urologie
The Czech Urological Society	The Slovak Urological Society
The Danish Urological Society	The Slovenian Urological Association
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The Finnish Urological Association	The Swedish Urology Association
The French Association of Urology	The Swiss Society of Urology
The German Urological Association	The Taiwan Urological Association
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The Hungarian Urological Association	The Thai Urological Association
The Icelandic Urological Association	The Urological Society of India
The Indonesian Urological Association	The Urological Association of Serbia
The Irish Society of Urology	The Ukrainian Association of Urology

Furthermore, the EAU Guidelines Office is most grateful for the continued support of the European Board of Urology.



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Non-muscle-invasive (Ta, T1 and CIS) Bladder Cancer

Upper Urinary Tract Urothelial Cell Carcinomas

Muscle-Invasive and Metastatic Bladder Cancer

Primary Urethral Carcinoma

Prostate Cancer

Renal Cell Carcinoma

Testicular Cancer

Penile Cancer

**Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS),
incl. benign prostatic obstruction (BPO)**

Urinary Incontinence

Neuro-Urology

Erectile dysfunction, Premature ejaculation, Penile Curvature and Priapism

Male Infertility

Male Hypogonadism

Urological Infections

Urolithiasis

Paediatric Urology

Urological Trauma

Chronic Pelvic Pain

Renal Transplantation

Thromboprophylaxis

Abbreviations

EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

M. Babjuk (Chair), M. Burger (Vice-Chair), E. Compérat,
P. Gontero, A.H. Mostafid, J. Palou, B.W.G. van Rhijn,
M. Rouprêt, S.F. Shariat, R. Sylvester, R. Zigeuner
Guidelines Associates: O. Capoun, D. Cohen,
V. Hernández, V. Soukup

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1. INTRODUCTION

1.1 Aim and scope

This overview represents the updated European Association of Urology (EAU) guidelines for Non-muscle-invasive Bladder Cancer (NMIBC), TaT1 and carcinoma *in situ* (CIS). The information presented is limited to urothelial carcinoma, unless specified otherwise. The aim is to provide practical recommendations on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

Separate EAU guidelines documents are available addressing upper tract urothelial carcinoma (UTUC) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma [3]. It must be emphasised that clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a pathologist and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of suffering from bladder cancer. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: <https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/>.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the NMIBC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2016 [4], as are a number of translations of all versions of the EAU NMIBC Guidelines. All documents are accessible through the EAU website Uroweb: <https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU Guidelines on Bladder Cancer were first published in 2000. This 2017 NMIBC guidelines document presents a limited update of the 2016 publication.

1.4.2 Summary of changes

New references have been added throughout the 2017 NMIBC Guidelines document.

Key changes in this 2017 print:

- Section 4.3 - T1 subclassification. This is a new section.
- Section 5.5 - Urinary Cytology. Diagnostic categories based on the Paris Working Group Classification have been added.
- Section 5.10.2 - Surgical and technical aspects of tumour resection. This section has been revised and enlarged, resulting in changes in the recommendations (Section 5.14).
- Section 5.12 - Second resection. Additional literature has been included, resulting in changes in the recommendations (Section 5.14).
- Section 6.4 - Subgroup of highest risk tumours. This is a new section.
- Section 7.2.1.3.2 - Device-assisted intravesical chemotherapy. This is a new section.

Changes in recommendations

Section 5.9: A new recommendation has been added.

Recommendations for the primary assessment of NMIBC	GR
Repeat urine cytology in patients with suspicious initial cytology results.	C

Section 5.14: Additional information has been included.

Recommendations for transurethral resection of the bladder (TURB) and/or biopsies and pathology report	
Perform <i>en-block</i> resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). The presence of detrusor muscle in the specimen is required in all cases except for TaG1/LG tumours.	B
Perform a second TURB in the following situations: <ul style="list-style-type: none"> • after (suspicion of) incomplete initial TURB (in the case of any doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with exception of TaLG/G1 tumours and primary CIS; • In T1 tumours. 	A
Register the results of a second TURB as it reflects the quality of the initial resection.	A

Section 7.5: A new recommendation have been included.

Recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS	GR
In patients with bacillus Calmette-Guérin failure, who are not candidates of radical cystectomy due to comorbidities, use preservation strategies (device-assisted instillations of chemotherapy, intravesical chemotherapy, intravesical immunotherapy).	C

Section 8.1: A new recommendation has been added.

Recommendations for follow-up of patients after transurethral resection of the bladder for NMIBC	GR
In patients initially diagnosed with TaLG/G1-2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible, or refused by the patient.	C

2. METHODS

2.1 Data Identification

For the 2017 NMIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the NMIBC Guidelines was performed. Excluded from the search were basic research studies, case series, reports and editorial comments. Only articles published in the English language, addressing adults, were included. The search was restricted to articles published between June 1st 2015 and April 22nd 2016. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 973 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available on line:

<https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications>.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>. A list of Associations endorsing the EAU Guidelines can also be viewed on line at the above address.

2.2 Review

Chapter 7, Disease Management was peer reviewed prior to publication in 2016. All other chapters of the NMIBC Guidelines were peer-reviewed in 2015.

2.3 Future goals

The results of an ongoing systematic review will be included in the 2018 update of the NMIBC Guidelines. These reviews are performed using standard Cochrane systematic review methodology; <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>.

Ongoing systematic review:

1. Is there a difference between the 2004 WHO grading system and the 1973 WHO grading system for NMIBC in terms of prognostic performance and reproducibility? [6].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered [7]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [7]. In the European Union the age-standardised incidence rate is 19.1 for men and 4.0 for women [7]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [7]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, partly caused by the different methodologies used and the quality of data collection [8]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [9].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1); in younger patients (< 40) this percentage is even higher [10]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to T2-4 tumours [7, 8].

3.2 Aetiology

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [8, 9, 11] (LE: 3). Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants, which process paint, dye, metal and petroleum products [8, 9, 12, 13]. In developed industrial settings, these risks have been reduced by work-safety guidelines, therefore, chemical workers no longer have a higher incidence of BC compared to the general population [8, 12, 13].

While family history seems to have little impact [14] and, to date, no overt significance of any genetic variation for BC has been shown, genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors [8, 15, 16].

Although the significance of fluid intake is uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, also exposure to arsenic in drinking water increases risk [8, 17] (LE: 3). The association between personal hair dye use and risk remains uncertain; an increased risk has been suggested in users of permanent hair dyes with a slow NAT2 acetylation phenotype [8]. Dietary habits seem to have little impact [18-20].

Exposure to ionizing radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [8, 17] (LE: 3). Schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, is also a cause of BC [8] (LE: 3).

3.3 Pathology

The information presented in this text is limited to urothelial carcinoma, unless otherwise specified.

3.4 Summary of evidence for epidemiology, aetiology and pathology

Summary of evidence	LE
Worldwide, bladder cancer is the eleventh most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of bladder cancer diagnosis have been identified.	3

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the Tumour, Node, Metastasis (TNM) classification system [21]. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis). These tumours can be treated by transurethral resection of the bladder (TURB), eventually in combination with intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. However, molecular biology techniques and clinical experience have demonstrated the highly malignant potential of CIS and T1 lesions as compared to Ta lesions. The terms “NMIBC” and “superficial BC” are therefore suboptimal descriptions.

4.2 Tumour, Node, Metastasis Classification (TNM)

The 2009 TNM classification approved by the Union International Contre le Cancer (UICC) was updated in 2017 (8th Edn.), but with no changes in relation to bladder tumours (Table 4.1) [21].

Table 4.1: 2017 TNM classification of urinary bladder cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : ‘flat tumour’
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastases

4.3 T1 subclassification

The depth and extent of invasion into the lamina propria (T1 substaging) has been demonstrated to be of prognostic value in retrospective cohort studies [22, 23] (LE: 3). Its use is recommended by the most recent 2016 World Health Organization (WHO) classification [24]. The optimal system to substage T1 remains to be defined.

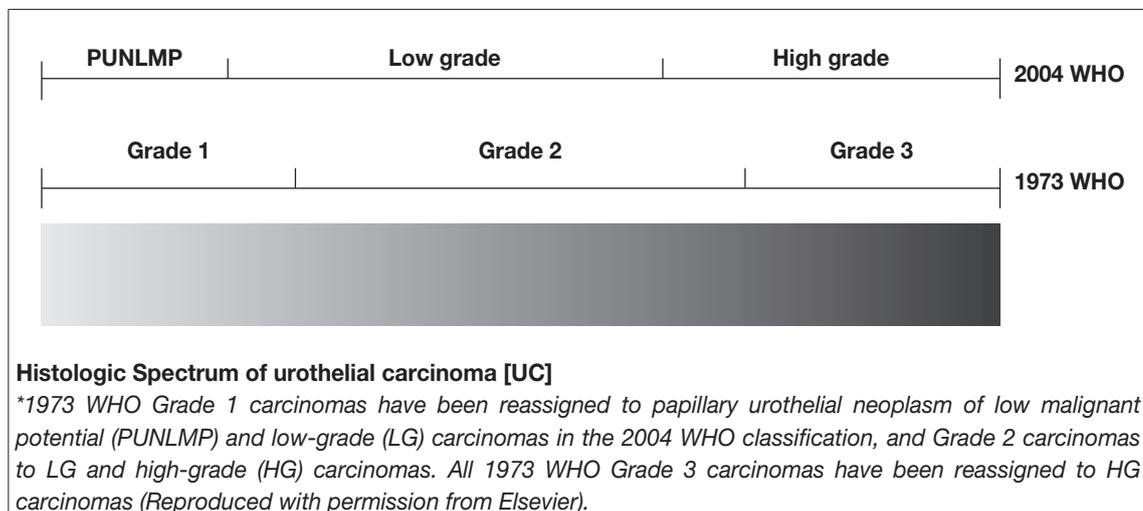
4.4 Histological grading of non-muscle-invasive bladder urothelial carcinomas

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of urothelial carcinomas which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [25, 26] (Tables 4.2 and 4.3, Fig 4.1). Recently an update of the 2004 WHO grading classification was published [24] but the following guidelines are still based on the 1973 and 2004 WHO classifications since most published data rely on these two classifications [25, 26].

Table 4.2: WHO grading in 1973 and in 2004 [25, 26]

<p>1973 WHO grading</p> <p>Grade 1: well differentiated</p> <p>Grade 2: moderately differentiated</p> <p>Grade 3: poorly differentiated</p> <p>2004 WHO grading system (papillary lesions)</p> <p>Papillary urothelial neoplasm of low malignant potential (PUNLMP)</p> <p>Low-grade (LG) papillary urothelial carcinoma</p> <p>High-grade (HG) papillary urothelial carcinoma</p>
--

The prognostic value of both WHO 1973 and 2004 grading systems has been confirmed. Attempts to demonstrate better prognostic value of one over the other, however, have yielded controversial results [27-29]. (LE: 2a). Moreover, the 2004 WHO system have not been fully incorporated into prognostic models yet.

Figure 4.1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications [30]*

4.5 Carcinoma *in situ* and its classification

Carcinoma *in situ* (CIS) is a flat, high-grade, non-invasive urothelial carcinoma. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. Carcinoma *in situ* is often multifocal and can occur in the bladder, but also in the upper urinary tract, prostatic ducts, and prostatic urethra [31].

Classification of CIS according to clinical type [32]:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

Table 4.3: WHO 2004 histological classification for flat lesions

<ul style="list-style-type: none"> • Urothelial proliferation of uncertain malignant potential (flat lesion without atypia or papillary aspects). • Reactive atypia (flat lesion with atypia). • Atypia of unknown significance. • Urothelial dysplasia. • Urothelial CIS is always high grade.
--

4.6 Inter- and intra-observer variability in staging and grading

There is significant variability among pathologists for the diagnosis of CIS, for which agreement is achieved in only 70-78% of cases [33] (LE: 2a). There is also interobserver variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2004 classifications. The general conformity in staging and grading is between 50% and 60% [28, 34-36] (LE: 2a). The published comparisons have not clearly confirmed that the WHO 2004 classification provides better reproducibility than the 1973 classification [27, 28, 36, 37].

4.7 Further pathology parameters

According to a meta-analysis of retrospective trials, the presence of lymphovascular invasion (LVI) in TURB specimens is connected with an increased risk of pathological upstaging [38] (LE: 3). Lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours [38] (LE: 3). Some variants of urothelial carcinoma (micropapillary, plasmocytoid, nested, sarcomatoid, microcystic, squamous and adeno variants, have a worse prognosis than classical urothelial carcinoma [2, 39-46] (LE: 3).

Molecular markers, particularly FGFR3 mutation status, are promising but need further validation [47-51].

4.8 Summary of evidence and recommendations for bladder cancer classification

Summary of evidence	LE
The depth of invasion (staging) is classified according to the TNM classification.	2a
Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis).	2a
T1 and CIS, as compared to Ta, have high malignant potential, the term non-muscle-invasive bladder cancer (NMIBC) is therefore a suboptimal description.	3
For histological classification of NMIBC, both the WHO 1973 and 2004 grading systems are used.	2a

Recommendations	GR
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	A
Use both the 1973 and 2004/2016 WHO grading systems for histological classification.	A
Do not use the term "superficial bladder cancer".	A
Mention the tumour stage and grade whenever the terminology NMIBC is used in individual cases.	A

5. DIAGNOSIS

5.1 Patient history

A comprehensive patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher stage disease compared to non-visible haematuria at first presentation [52]. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding.

5.3 Physical examination

Physical examination does not reveal NMIBC.

5.4 Imaging

5.4.1 Computed tomography urography and intravenous urography

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, indicated by filling defects or hydronephrosis.

Intravenous urography (IVU) is an alternative if CT is not available [53] (LE: 3), but particularly in muscle-invasive tumours of the bladder and in UTUCs, CT urography gives more information than IVU (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography or IVU once a bladder tumour has been detected is questionable due to the low incidence of significant findings obtained [54-56] (LE: 2a). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [55] (LE: 2b). The risk of UTUC during follow up increases in patients with multiple- and high-risk tumours [57] (LE: 3).

5.4.2 Ultrasound (US)

Transabdominal US permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder [58] (LE: 3). Ultrasound is therefore a useful tool for detection of obstruction in patients with haematuria. However, it cannot exclude the presence of UTUC and cannot replace CT urography.

The diagnosis of CIS cannot be made with imaging methods (CT urography, IVU or US) (LE: 4).

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in G3 and high-grade tumours (84%), but low sensitivity in G1 and low-grade tumours (16%) [59]. The sensitivity in CIS detection is 28-100% [60] (LE: 2b). Cytology is useful, particularly as an adjunct to cystoscopy, if G3/CIS malignancy is present. Positive voided urinary cytology can indicate an urothelial tumour anywhere in the urinary tract; negative cytology, however, does not exclude the presence of a tumour.

Cytological interpretation is user-dependent [61]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, but in experienced hands specificity exceeds 90% [61] (LE: 2b).

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [62]:

- Adequacy of urine specimens (Adequacy);
- Negative for high-grade urothelial carcinoma (Negative);
- Atypical urothelial cells (AUC);
- Suspicious for high-grade urothelial carcinoma (Suspicious);
- High-grade urothelial carcinoma (HGUC);
- Low-grade urothelial neoplasia (LGUN).

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [63]. In patients with suspicious cytology repeat investigation is advised [64] (LE: 3).

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests were developed [65-69]. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines. A list of the more established urine tests (US Food and Drug Administration [FDA] approved and those for which multi-institutional data are available) is listed in Table 5.1.

The following conclusions can be drawn regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity, compared to urine cytology [65, 67-72] (LE: 3).
- Benign conditions and bacillus Calmette-Guérin (BCG) influence many urinary marker tests [65-69] (LE: 3).
- Requirements for sensitivity and specificity of a urinary marker test depend on the clinical context of the patient (screening, primary detection, follow up [high risk, low/intermediate risk]) [67, 68, 73] (LE: 3).
- Patient selection explains the wide range in performance of the markers listed in Table 5.1.
- Positive results of Cytology, UroVysion (FISH), NMP-22, Ucyt+ and microsatellite analysis in patients with negative cystoscopy and upper tract workup, may identify patients more likely to experience recurrence [74-77] and possibly progression [74-78] (LE: 3).

Table 5.1: Summary of more established urinary markers

Markers (or test specifications)	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumours (%)	Point-of-care test	LE
UroVysion (FISH)*	30-86	63-95	66-70	No	2b
Microsatellite analysis	58-92	73-100	90-92	No	1b
Immunocyt/uCyt +*	52-100	63-79	62-92	No	2a
Nuclear matrix Protein 22*	47-100	55-98	75-92	Yes	2a
BTA stat*	29-83	56-86	62-91	Yes	3
BTA TRAK*	53-91	28-83	74-77	No	3
Cytokeratins	12-88	73-95	33-100	No	3

BTA = bladder tumour antigen.

** FDA approved.*

5.7 Potential application of urinary cytology and markers

The following objectives of urinary cytology or molecular tests must be considered.

5.7.1 Screening of the population at risk of bladder cancer

The application of haematuria dipstick, NMP22 or UroVysion in BC screening in high-risk populations has been

reported [79]. The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness [77, 79]. Routine screening for BC is not recommended [80].

5.7.2 **Exploration of patients after haematuria or other symptoms suggestive of bladder cancer (primary detection)**

It is generally accepted that none of the currently available tests can replace cystoscopy. However, urinary cytology or markers can be used as an adjunct to cystoscopy to detect invisible tumours, particularly CIS. In this setting, sensitivity for high-grade tumours and specificity are particularly important. Urinary cytology is highly specific, but urinary markers lack such high specificity and are not recommended for primary detection.

5.7.3 **Surveillance of non-muscle-invasive bladder cancer**

Research has been carried out into the usefulness of urinary cytology vs. markers in the follow up of NMIBC [69, 81, 82].

5.7.3.1 *Follow-up of high-risk non-muscle-invasive bladder cancer*

High-risk tumours should be detected early in follow up, and the percentage of tumours missed should be as low as possible. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology.

5.7.3.2 *Follow-up of low/intermediate-risk non-muscle-invasive bladder cancer*

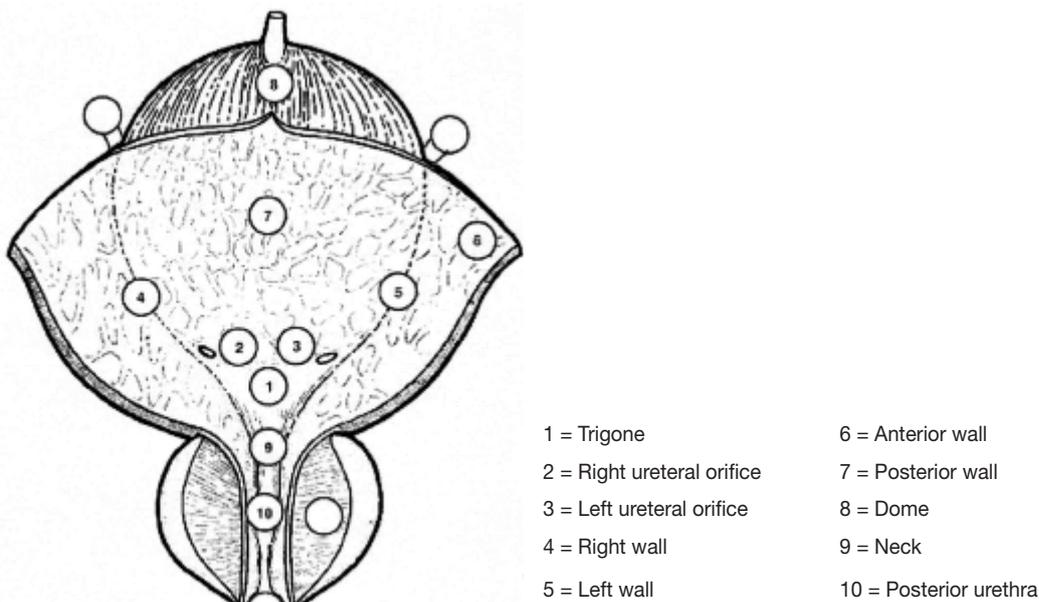
To reduce the number of cystoscopy procedures, urinary markers should be able to detect recurrence before the tumours are large and numerous. The limitation of urinary cytology is its low sensitivity for low-grade recurrences. Several urinary markers are better, but still do not detect half of the low-grade tumours identified by cystoscopy [67] (LE: 3).

According to current knowledge, no urinary marker can replace cystoscopy during follow up or help to lower cystoscopy frequency in a routine fashion. One prospective randomised study found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [83] (LE: 1b), supporting the adjunctive role of a non-invasive urine test performed before follow-up cystoscopy [83].

5.8 **Cystoscopy**

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue by either cold-cup biopsy or resection. Carcinoma *in situ* is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies [84]. Cystoscopy is initially performed as an outpatient procedure. A flexible instrument with topical intra-urethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [85].

Figure 5.1: Bladder diagram



5.9 Summary of evidence and recommendations for the primary assessment of non-muscle-invasive bladder cancer

Summary of evidence	LE
The diagnosis of bladder cancer depends on cystoscopy examination.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma <i>in situ</i> .	2b

Recommendations	GR
Take a patient history.	A
Renal and bladder ultrasound may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of non-muscle-invasive bladder cancer (NMIBC), perform computed tomography urography (or intravenous urography [IVU]) in selected cases (e.g., tumours located in the trigone, multiple or high-risk tumours).	B
Perform cystoscopy in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology or by any other non-invasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended (see Figure 5.1).	C
Voided urine cytology is advocated as an adjunct to cystoscopy to detect high-grade tumour.	C
Perform cystoscopy on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C
Repeat urine cytology in patients with suspicious initial cytology results.	C

5.10 Transurethral resection of TaT1 bladder tumours

5.10.1 Strategy of the procedure

The goal of TURB in TaT1 BC is to make the correct diagnosis and completely remove all visible lesions. It is a crucial procedure in the diagnosis and treatment of BC. TURB should be performed systematically in individual steps (see Section 5.14).

5.10.2 Surgical and technical aspects of tumour resection

5.10.2.1 Surgical strategy of resection (resection in fractions, *en-bloc* resection)

A complete resection is essential to achieve a good prognosis [86]. A complete resection can be achieved by either resection in fractions or *en-bloc* resection.

- Resection in fractions (separate resection of the exophytic part of the tumour, the underlying bladder wall and the edges of the resection area) provides good information about the vertical and horizontal extent of the tumour [87] (LE: 3).
- *En-bloc* resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser is feasible in selected exophytic tumours. It provides high quality resected specimens with the presence of detrusor muscle in 96-100% of cases [88-91] (LE 3).

The technique selected is dependent on the size and location of the tumour and experience of the surgeon.

5.10.2.2 Evaluation of resection quality

It has been confirmed that the absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence and tumour understaging [92] (LE: 2b). The presence of detrusor muscle in the specimen is considered as the surrogate criterion of the resection quality and is required (except of TaG1/LG tumours). It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [93].

5.10.2.3 Monopolar and bipolar resection

Compared to monopolar resection, bipolar resection has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and to produce better specimens for the pathologist [94] (LE: 3). Currently, the results remain controversial [95-97].

5.10.2.4 Office-based fulguration and laser vaporisation

In patients with a history of small, TaLG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and is a treatment option [94, 98] (LE: 3). There are no prospective comparative studies assessing the oncological outcomes.

Potassium titanyl-phosphate (KTP) laser vaporisation is associated with a low risk of complications. Its oncologic outcomes need to be confirmed in a larger patient population [99].

5.10.2.5 *Resection of small papillary bladder tumours at the time of transurethral resection of the prostate (TURP)*

Only limited, retrospective, data exist on the outcome of incidentally detected papillary bladder tumour during cystoscopy as the initial step of TURP. Provided these tumours are papillary by aspect, rather small and not extensively multifocal, it seems feasible to resect these tumours and continue with the resection of the prostate. However, no exact risk-assessment can be provided [100, 101].

5.10.3 **Bladder and prostatic urethral biopsies and incidental papillary tumours during transurethral resection of the prostate**

Carcinoma *in situ* can present as a velvet-like, reddish, area indistinguishable from inflammation, or it may not be visible at all. For this reason, the strategy of taking biopsies from abnormal urothelium and biopsies from normal-looking mucosa (random/mapping biopsies) is recommended (see Section 5.14). The indication for random biopsies reflects the very low likelihood of detecting CIS, especially in low-risk tumours (< 2%) [102] (LE: 2a). The risk increases in patients with high-risk tumours and with positive cytology [103].

If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy (see Section 5.11.1).

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.* [104] showed that in 128 men with T1G3 BC, the incidence of CIS in the prostatic urethra was 11.7% (LE: 2b). The risk of prostatic urethra or duct involvement is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [105] (LE: 3). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases (see recommendation in Section 5.14) [104, 106].

5.11 **New methods of tumour visualisation**

As a standard procedure, cystoscopy and TURB are performed using white light. However, the use of white light can lead to missing lesions that are present but not visible, which is why new technologies are being developed.

5.11.1 **Photodynamic diagnosis (fluorescence cystoscopy)**

Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly for CIS [107, 108] (LE: 2a). In a systematic review and meta-analysis, PDD had higher sensitivity than white light endoscopy in the pooled estimates for analyses at both the patient-level (92% vs. 71%) and biopsy-level (93% vs. 65%) [108]. A prospective randomised trial did not confirm a higher detection rate in patients with known positive cytology before TURB [109].

Photodynamic diagnosis had lower specificity than white-light endoscopy (63% vs. 81%) [108].

False-positivity can be induced by inflammation or recent TURB and during the first three months after BCG instillation [110, 111] (LE: 3). Prospective randomised studies evaluating the impact of ALA fluorescence-guided (FC) TURB on disease-recurrence rate provided controversial results [108, 112, 113].

The beneficial effect of HAL FC on recurrence rate in patients with TURB was confirmed by a multicentre, prospective, randomised trial and by a raw-data-based meta-analysis of controlled trials. A meta-analysis reported in the HAL arms an increase in detection of tumour lesions across all risk groups and an absolute reduction of < 10% in recurrence rates within twelve months [114] (LE: 1a). The beneficial effect of HAL FC on recurrence rate in patients with TURB and early intravesical instillation of chemotherapy was not confirmed by two prospective randomised trials [115, 116]. In the prospective controlled analysis of patients receiving early instillation in a real-life clinical setting, the beneficial effect of HAL FC on early recurrence rate was confirmed for low- and intermediate-risk tumours [117]. The value of fluorescence-guided TURB for the improvement of outcome in relation to progression rate, survival and clinical management remains to be demonstrated.

5.11.2 **Narrow-band imaging**

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Initial studies have demonstrated improved cancer detection by NBI-guided biopsies and resection [118, 119] (LE: 3). The reduction of recurrence rate if NBI is used during TURB has been confirmed after three and twelve months only for low-risk tumours (pTaLG, < 30 mm, no CIS) [120].

5.12 Second resection

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [86] (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-55% of patients, after resection of TaG3 tumour in 41.4% [121-124]. Moreover, the tumour is often understaged in the initial resection. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumour ranges from 1.3-25%, and increases to 45% if there was no muscle in the initial resection [109, 125-128]. This risk increased to 50% in some radical cystectomy (RC) series, although these studies only enrolled selected patients [129-131] (LE: 2a). Treatment of a TaT1 high-grade tumour and a T2 tumour is completely different; correct staging is therefore important. It has been demonstrated that a second TURB can increase recurrence-free survival [121, 122] (LE: 2a), improve outcomes after BCG treatment [132] (LE: 3) and provide prognostic information [127, 129, 133] (LE: 3).

In a retrospective evaluation of a large multi-institutional cohort of 2,451 patients with BCG-treated T1G3/HG tumours (second resection was performed in 935 patients), the second resection improved recurrence-free survival (RFS), progression-free survival (PFS) and overall survival (OS) only in patients without muscle in the specimen from initial resection [134] (LE:3).

Retrospective evaluation showed that a second resection performed 14-42 days after initial resection provides longer RFS and PFS comparing to second resection performed after 43-90 days [135] (LE:3). Based on these arguments, a second TURB is recommended in selected cases two-six weeks after initial resection (for recommendations on patient selection, see Section 5.14).

The results of the second resection (residual tumours and understaging) reflect the quality of the initial TURB. As the goal is to improve the quality of the initial TURB, the results of the second resection should be recorded.

5.13 Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the diagnosis and treatment decision-making process for BC. Close co-operation between urologists and pathologists is required. A high quality of resected and submitted tissue and clinical information is essential for correct pathological assessment. The presence of sufficient muscle is necessary for the correct assignment of the T category. To obtain all relevant information, the specimen collection, handling and evaluation should respect the recommendations provided below (see Section 5.14) [136].

5.14 Summary of evidence and recommendations for transurethral resection of the bladder, biopsies and pathology report

Summary of evidence	LE
Transurethral resection of the bladder (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the treatment of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour understaging.	2b
In patients with a history of small, TaLG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis is feasible and safe.	3
A second TURB can detect residual tumours and tumour understaging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2

Recommendations	GR
In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	A
Perform TURB systematically in individual steps: <ul style="list-style-type: none"> • bimanual palpation under anaesthesia; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen for pathology evaluation. 	C

Performance of individual steps	
Perform <i>en-block</i> resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). The presence of detrusor muscle in the specimen is required in all cases except for TaG1/LG tumours.	B
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	C
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder wall) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance). If equipment is available, perform fluorescence-guided (PDD) biopsies.	B
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma <i>in situ</i> is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between the 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	C
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C
The TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	C
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (random biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (prostatic urethra biopsy).	C
Perform a second TURB in the following situations: <ul style="list-style-type: none"> • after (suspicion of) incomplete initial TURB (in the case of any doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with the exception of TaLG/G1 tumours and primary CIS; • in T1 tumours. 	A
If indicated, perform a second TURB within two-six weeks after initial resection. This second TURB should include resection of the primary tumour site.	C
Register the results of a second TURB as it reflects the quality of the initial resection.	A
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	A
Pathological report	
The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.	A
The pathological report should specify the presence of lymphovascular invasion or unusual (variant) histology.	C
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

In order to predict, separately, the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group has developed a scoring system and risk tables [137]. The basis for these tables are individual patient data from 2,596 patients diagnosed with TaT1 tumours, who were randomised into seven EORTC trials. Patients with CIS alone were not included. Seventy-eight percent of patients received intravesical treatment, mostly chemotherapy. However, they did not undergo a second TURB or receive maintenance BCG.

The scoring system is based on the six most significant clinical and pathological factors which are shown in Table 6.1. It also illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 6.2 shows the total scores stratified, into four categories that reflect various probabilities of recurrence and progression at one and five years [137] (LE: 2a).

Table 6.1: Weighting used to calculate disease recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	0-17	0-23

Table 6.2: Probability of recurrence and disease progression according to total score

Recurrence score	Probability of recurrence at 1 year	Probability of recurrence at 5 years		
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Progression score	Probability of progression at 1 year	Probability of progression at 5 years		
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

NB: Electronic calculators for Tables 6.1 and 6.2, which have been updated for the Apple and Android phones and tablets, are available at <http://www.eortc.be/tools/bladdercalculator/>.

A scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression has been published by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received twelve instillations over five to six months. No immediate post-operative instillation or second TURB was performed in these patients. The scoring system is based on the evaluation of seven prognostic factors:

- gender;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- tumour grade.

Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [138] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this sample, which is a more effective instillation therapy. The CUETO risk calculator is available at: <http://www.aeu.es/Cueto.html>.

The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG and by long-term follow up in an independent patient population [139, 140] (LE: 2a). In 1,812 intermediate- and high-risk patients without CIS treated with one to three years of maintenance BCG, the EORTC found that the prior disease-recurrence rate and number of tumours were the most important prognostic factors for disease recurrence, stage and grade were the most important prognostic factors for disease progression and disease-specific survival, while age and grade were the most important prognostic factors for OS. T1G3 patients do poorly, with one- and five-year disease-progression rates of 11.4% and 19.8%, respectively. Using these data the new EORTC risk groups and nomograms for BCG treated patients were designed [141] (LE: 2a).

Further prognostic factors have been described in selected patient populations:

- In T1G3 tumours important prognostic factors were female sex and CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with induction course only) [104, 142] (LE: 2b).
- Attention must be given to patients with T1G3 tumours in bladder (pseudo) diverticulum because of the absence of muscle layer in the diverticular wall [143] (LE: 3).
- In patients with high-risk disease, the tumour stage at the time of the second TURB is an unfavourable prognostic factor [129, 133] (LE: 3)
- In patients with T1G2 tumours treated with TURB, recurrence at three months was the most important predictor of progression [144] (LE: 2b).
- The prognostic value of pathological factors has been discussed elsewhere (see Section 4.6). More research is needed to determine the role of molecular markers in improving the predictive accuracy of currently available risk tables [139, 145].

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [146] (LE: 3). Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease. Publications are based on retrospective analyses of small series of patients and conclusions are not homogeneous. Some studies have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [147, 148], extended CIS [149] and CIS in the prostatic urethra [104] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [138-140, 144]. Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders [150, 151] (LE: 2a).

6.3 Patient stratification into risk groups

To facilitate treatment recommendations it is important to categorise patients into risk groups. Based on available prognostic factors and in particular data from the EORTC risk tables, the Guidelines Panel recommends stratification of patients into three risk groups. Table 6.3 provides a definition of these risk groups, which takes into account the EORTC risk tables' probabilities of recurrence and especially progression.

6.4 Subgroup of highest-risk tumours

Based on prognostic factors, it is possible to substratify high-risk group patients, and identify those that are at the highest risk of disease progression. Patients diagnosed with T1G3/HG tumours associated with concurrent bladder CIS, multiple and/or large T1G3/HG tumours and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma and T1 tumours with LVI (Table 6.3) are at the highest risk of progression.

Table 6.3: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG*), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high risk).
High-risk tumours	Any of the following: <ul style="list-style-type: none"> • T1 tumour • G3 (HG**) tumour • carcinoma <i>in situ</i> (CIS) • Multiple, recurrent and large (> 3 cm) TaG1G2 /LG tumours (all features must be present)*. <p>Subgroup of highest risk tumours: T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion.</p>

Substratification of high-risk tumours for clinical purposes is addressed in Table 7.2.

*Low grade is a mixture of G1 and G2.

** High grade is a mixture of some G2 and all G3 (see Figure 4.1).

6.5 Summary of evidence and recommendations for stratification of non-muscle-invasive bladder cancer

Summary of evidence	LE
The EORTC scoring system and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with non-muscle-invasive bladder cancer (NMIBC).	2a
In patients treated with BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression.	2a
In patients receiving BCG maintenance: prior recurrence rate and number of tumours are the most important prognostic factors for disease recurrence.	2a
Stage and grade are the most important prognostic factors for disease progression and disease specific survival.	2a
Patient age and grade are the most important prognostic factors for overall survival.	2a

Recommendations	GR
Stratify patients into three risk groups according to Table 6.3.	B
Apply the EORTC risk tables and calculator for the prediction of the risk of tumour recurrence and progression in different intervals after transurethral resection of the bladder, in individual patients.	B
Use the CUETO risk tables and the new EORTC risk groups for the prediction of the risk of tumour recurrence and progression in individual patients treated with bacillus Calmette-Guérin.	B

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression [152, 153] (LE: 3). While it is still controversial whether smoking cessation in BC will favourably influence the outcome of BC treatment, patients should be counselled to stop smoking due to the general risks connected with tobacco smoking [154-157] (LE: 3).

7.2 Adjuvant treatment

7.2.1 Intravesical chemotherapy

Although TURB by itself can eradicate a Ta, T1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the three-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [86]. It is therefore necessary to consider adjuvant therapy in all patients.

7.2.1.1 A single, immediate, post-operative intravesical instillation of chemotherapy

Immediate single instillation (SI) has been shown to act by destroying circulating tumour cells after TURB, and by an ablative effect (chemo resection) on residual tumour cells at the resection site and on small overlooked tumours [158-161] (LE: 3).

Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that after TURB, SI significantly reduces the recurrence rate compared to TURB alone [162-165] (LE: 1a). In the most recent systematic review and individual patient data meta-analysis of 2,278 eligible patients [162], SI reduced the five-year recurrence rate by 14%, from 59% to 45%. The number to treat (NNT) to prevent one recurrence within five years was seven eligible patients. Only patients with a prior recurrence rate of less than or equal to one recurrence per year and those with an EORTC recurrence score < 5 benefited from SI. In patients with an EORTC recurrence score ≥ 5 and/or patients with a prior recurrence rate of > 1 recurrence per year, SI was not effective as a single adjuvant treatment. Mitomycin C (MMC), epirubicin, and pirarubicin have all shown a beneficial effect [162]. No randomised comparisons of individual drugs have been conducted [162-165] (LE: 1a).

Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by extracellular matrix [158, 166, 167] (LE: 3). In all SI studies, the instillation was administered within 24 hours. To maximise the efficacy of SI, one should devise flexible practices that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre. As severe complications have been reported in patients with drug extravasation [168, 169] safety measures should be maintained (see Section 7.5).

7.2.1.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1, 6.2 and 6.3), a SI reduces the risk of recurrence and is considered to be the standard and complete treatment [162, 163] (LE: 1a). For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1, 6.2 and 6.3). The individual patient data meta-analysis also showed that a SI reduced recurrences in intermediate-risk patients with an EORTC recurrence score < 5, none of whom received further treatment prior to recurrence [162]. There is evidence from several studies in intermediate-risk patients that SI might have an impact on recurrence even when further adjuvant instillations are given; however, they do not take into account the EORTC recurrence score [170-172] (LE: 2a). In one study [173], further chemotherapy instillations after SI improved recurrence-free survival in intermediate-risk patients (LE: 2a). Conversely, a sufficient number of delayed repeat chemotherapy instillations without SI can also reduce recurrences [170, 172].

A large meta-analysis of 3,703 patients from eleven randomised trials showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [174]. This

corresponds to an absolute difference of 13-14% in the number of patients with recurrence. Contrary to these findings, two meta-analyses have demonstrated that BCG therapy may reduce the risk of tumour progression [175, 176] (LE: 1a) (see Section 7.2.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [177-179] (see Section 7.2.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy [179] (LE: 1a).

The length and frequency of chemotherapy instillations is still controversial. A systematic review of RCTs, comparing different schedules of intravesical chemotherapy instillations, concluded that the ideal duration and intensity of the schedule remains undefined because of conflicting data [172]. The available evidence does not support treatment longer than one year (LE: 3).

7.2.1.3 Options for improving efficacy of intravesical chemotherapy

7.2.1.3.1 Adjustment of pH, duration of instillation, and drug concentration

One RCT using MMC has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduced the recurrence rate [180] (LE: 1b). Another trial reported that duration of a one hour instillation of MCC was more effective compared to a 30 minute instillation, but no efficacy comparisons are available for one- vs. two-hour durations of instillation [181] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [182] (LE: 1b). In view of these data, instructions are provided (see Section 7.5).

7.2.1.3.2 Device-assisted intravesical chemotherapy

Hyperthermia

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [183]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate and high-risk bladder cancer, a reduced RFS at 24 months in the MMC group was demonstrated [184] (LE: 1b). Different technologies which increase the temperature of instilled MMC are available, however, data about their efficacy are still lacking.

Electromotive drug administration (EMDA)

The efficacy of MMC using EMDA in patients with high-risk tumours has been demonstrated in one small RCT [185]. The definitive conclusion however, needs further confirmation.

7.2.1.4 Summary of evidence - intravesical chemotherapy

Summary of evidence	LE
In patients with non-muscle-invasive bladder cancer and a prior low recurrence rate (\leq to one recurrence per year) and in those with an EORTC recurrence score < 5 , a single instillation (SI) significantly reduces the recurrence rate compared to transurethral resection of the bladder alone.	1a
In intermediate-risk patients, SI might have an impact on recurrence even when further adjuvant instillations are given.	3
Further chemotherapy instillations after SI improve recurrence-free survival in intermediate-risk patients.	2a

7.2.2 Intravesical bacillus Calmette-Guérin (BCG) immunotherapy

7.2.2.1 Efficacy of BCG

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB + chemotherapy for preventing the recurrence of NMIBC [177, 186-188] [189] (LE: 1a). Three recent RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin + interferon [190], MMC [191], or epirubicin alone [178] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long-lasting [178, 191] and was also observed in a separate analysis of patients with intermediate-risk tumours [178]. One meta-analysis [177] has evaluated the individual data from 2,820 patients enrolled in nine RCTs that have compared MMC vs. BCG. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance.

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [175, 176] (LE: 1a). A meta-analysis carried out by the EORTC-GUCG has evaluated data from 4,863 patients enrolled in 24 RCTs. Five different BCG strains were used, and in 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, in 260 out of 2,658 patients (9.8%) treated with BCG, tumours progressed, compared to 304 out of 2,205 (13.8%) in the control groups (TURB alone, TURB + intravesical chemotherapy, or TURB + other immunotherapy). This shows a reduction

of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS [176]. A recent RCT with long-term observation has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [178] (LE: 1b). On the contrary, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death [177].

The conflicting results in the outcomes of these studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. However, most studies showed a reduction in the risk of progression in high- and intermediate-risk tumours if BCG was applied including a maintenance schedule.

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [192]. In the most recent meta-analysis, however, BCG maintenance was more effective than MMC, both in patients previously treated and not previously treated with chemotherapy [177] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 years of age, but still more effective than epirubicin in a cohort of elderly patients [193] (LE: 1a).

7.2.2.2 *BCG strain*

The EORTC meta-analysis suggested no large differences in efficacy between various BCG strains [176]. Recently published smaller studies without maintenance demonstrated some differences between strains. This clearly needs further evaluation in prospective trials [194, 195] (LE: 2a).

7.2.2.3 *BCG toxicity*

BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy [176] (LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [196] (LE: 1b). It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [196]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [197]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [198] (LE: 2a).

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.5). The presence of leukocyturia, non-visible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [199, 200] (LE: 3).

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients; e.g. immunosuppression, human immunodeficiency virus [HIV] infection pose relative contraindications [201], although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients. The role of prophylactic anti-tuberculosis medication in these patients remains unclear [202-204] (LE: 3). The management of side effects after BCG should reflect their type and grade according to the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [205, 206] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical bacillus Calmette-Guérin (BCG) [206-209]

Management options for local side effects (modified from International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs)
	If symptoms improve within a few days: continue instillations
	If symptoms persist or worsen: <ol style="list-style-type: none"> Postpone the instillation Perform a urine culture Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: <ol style="list-style-type: none"> With positive culture: adjust antibiotic treatment according to sensitivity With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [207].
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis, if other symptoms present. If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for three months.
	Cessation of intravesical therapy.
Epididymo-orchitis [208]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.
Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or anti-tuberculosis drugs [209].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: <ul style="list-style-type: none"> High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily for 6 months. Early, high-dose corticosteroids as long as symptoms persist. Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or <i>Enterococcus</i>.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

7.2.2.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical six-weekly schedule introduced by Morales [210]. For optimal efficacy, BCG must be given in a maintenance schedule [175-177, 189] (LE: 1a). Many different maintenance schedules have been used, ranging from a total of ten instillations given in eighteen

weeks to 27 over three years [211]. The EORTC meta-analysis was unable to determine which BCG maintenance schedule was the most effective [176]. In their meta-analysis, Böhle *et al.* concluded that at least one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [175] (LE: 1a).

The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations is not fully known. Moreover, it can be different in each individual patient [212]. In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, three years' maintenance (three-weekly instillations 3, 6, 12, 18, 24, 30 and 36 months) reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or OS. In the three-year arm, however, 36.1% of patients did not complete the three-year schedule [213] (LE: 1b). In a RCT of 397 patients CUETO suggested that in high-risk tumours, the maintenance schedule with only one instillation every three months for three years may be suboptimal [214] (LE: 1b).

7.2.2.5 Optimal dose of BCG

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [215, 216] (LE: 1b). The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. One-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [217] (LE: 1b).

The EORTC did not find any difference in toxicity between one-third and full-dose BCG, but one third dose BCG was associated with a higher recurrence rate, especially when it was given only for one year [197, 213] (LE: 1b). The routine use of one-third dose BCG is complicated by potential technical difficulties in preparing the reduced dose reliably, given uneven distribution of colony-forming-units in the dry product formulation.

7.2.2.6 Indications for BCG

Although BCG is a very effective treatment, there is a consensus that not all patients with NMIBC should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends upon the patient's risk (Table 6.2). The recommendation for individual risk groups is provided in Section 7.5.

A statement by the Panel on BCG shortage can be accessed on line: <https://uroweb.org/guideline/non-muscleinvasive-bladder-cancer/?type=appendices-publications>.

7.2.2.7 Summary of evidence - BCG treatment

Summary of evidence	LE
In patients with intermediate- and high-risk tumours, intravesical bacillus Calmette-Guérin (BCG) after TURB reduces the risk of tumour recurrence; it is more effective than TURB alone or TURB + intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule.	1a
Three-year maintenance is more effective than one year to prevent recurrence in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

7.2.3 Combination therapy

In one RCT, a combination of MMC and BCG was shown to be more effective in reducing recurrences but more toxic compared to BCG monotherapy (LE: 1b). Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by one MMC instillation [218]. Another RCT in frequently recurrent NMIBC demonstrated significantly higher efficacy of weekly MMC followed by monthly BCG in reduction of the recurrence rate when compared to BCG and interferon [219] (LE: 1b). In contrast a recent RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and interferon for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [220] (LE: 1b). In an RCT using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy [185, 221] (LE: 2).

7.2.4 Specific aspects of treatment of Carcinoma in situ

7.2.4.1 Treatment strategy

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [137, 138], in this case further treatment according to the criteria summarised in Sections 7.2.1, 7.2.2, 7.3 and 7.4 is mandatory. CIS cannot be cured by an endoscopic procedure alone. Histological diagnosis of Carcinoma *in*

situ must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific-survival rates after immediate RC for CIS are excellent, but as many as 40-50% of patients might be over treated [146] (LE: 3).

7.2.4.2 Cohort studies on intravesical BCG or chemotherapy

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG [146-149, 222] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [149, 211, 222, 223] (LE: 3).

7.2.4.3 Prospective randomised trials on intravesical BCG or chemotherapy

Unfortunately, there have been few randomised trials in patients with CIS only. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [224] (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different immunotherapy [176] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [225]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1b).

7.2.4.4 Treatment of CIS in prostatic urethra and upper urinary tract

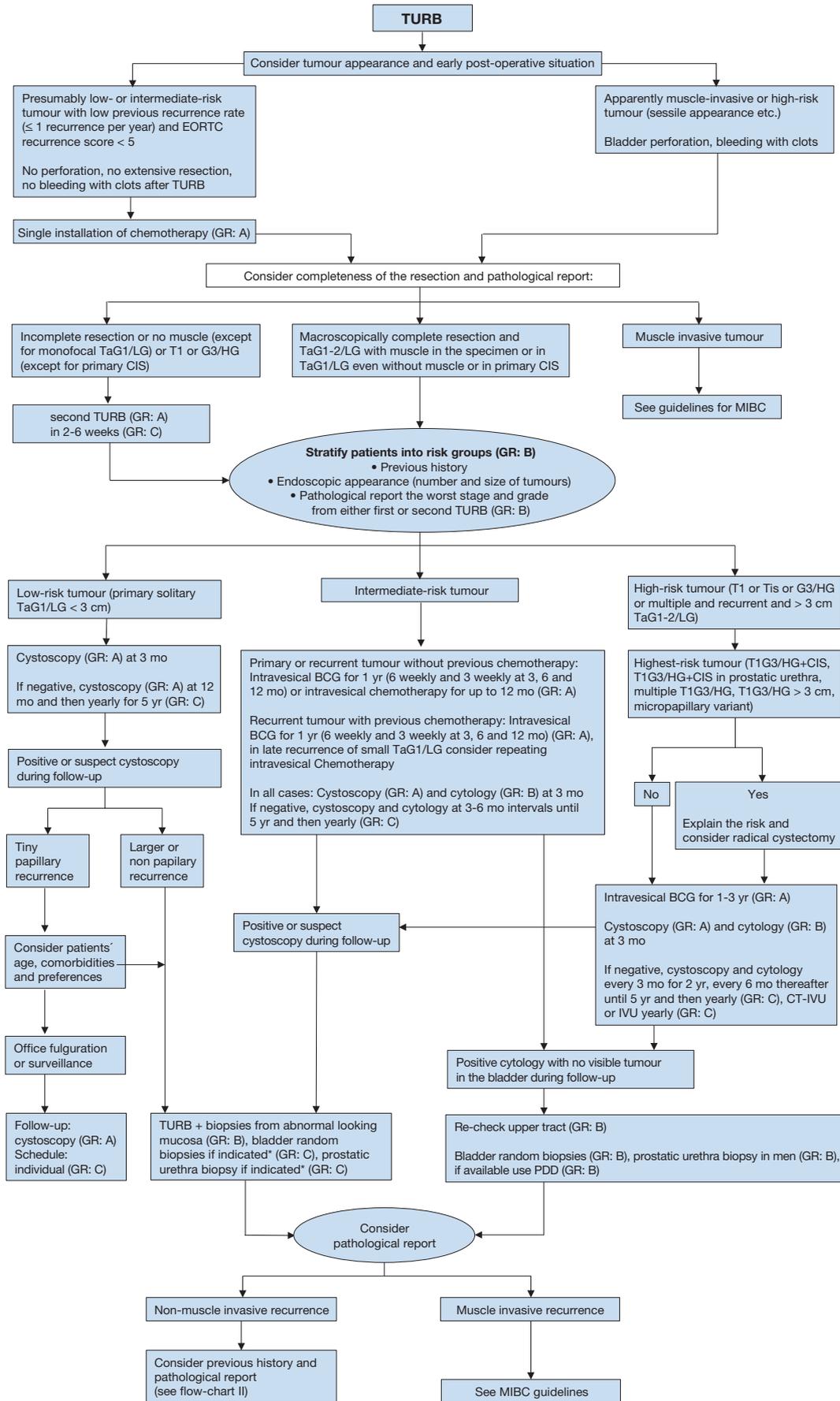
Patients with CIS are at high risk of extravesical involvement in the upper urinary tract (UUT) and in the prostatic urethra. Solsona *et al.* found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [226]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [226] (LE: 3). In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [31]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours), and for which immediate radical cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection of the prostate can improve contact of BCG with the prostatic urethra [85, 227] (LE: 3). However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

In patients with prostatic duct involvement, there are promising results after BCG instillation, but only from small series, so the data are insufficient to provide clear treatment recommendations and radical surgery should be considered [227, 228] (LE: 3). Treatment of CIS that involves the UUT is discussed in the EAU Guidelines on Urothelial Tumours of the Upper Urinary Tract [1].

7.2.4.5 Summary of evidence – treatment of carcinoma *in situ*

Summary of evidence	LE
Carcinoma <i>in situ</i> (CIS) cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, bacillus Calmette-Guérin treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression.	1b

Flowchart 7.1: Treatment strategy in primary or recurrent tumour(s) without previous BCG*



*For details and explanations see the text of the guidelines

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; GR = grade of recommendation; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.3 Treatment of failure of intravesical therapy

7.3.1 Failure of intravesical chemotherapy

Patients with NMIBC recurrence after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation [177] (LE: 1a).

7.3.2 Recurrence and failure after intravesical bacillus Calmette-Guérin (BCG) immunotherapy

Categories of unsuccessful treatment with intravesical BCG are presented in Table 7.2.

Table 7.2: Categories of unsuccessful treatment with intravesical BCG

BCG failure
Whenever a MIBC is detected during follow-up.
BCG-refractory tumour: 1. If high-grade, non-muscle-invasive papillary tumour is present at three months [229]. Further conservative treatment with BCG is associated with increased risk of progression [150, 230] (LE: 3). 2. If CIS (without concomitant papillary tumour) is present at both three and six months. If patients with CIS present at three months, an additional BCG course can achieve a complete response in > 50% of cases [31] (LE: 3). 3. If high-grade tumour appears during BCG therapy*.
High-grade recurrence after BCG. Recurrence of high-grade/grade 3 (WHO 2004/1973) tumour after completion of BCG maintenance, despite an initial response [231] (LE: 3).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [206].

* Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.

7.3.3 Treatment of BCG failure and recurrences after BCG

Treatment recommendations are provided in Sections 7.5 and 7.7. They reflect the categories mentioned in Table 7.2 and tumour characteristics at the time of recurrence.

Patients with BCG failure are unlikely to respond to further BCG therapy; RC is therefore the preferred option. Various studies suggest that repeat BCG therapy is appropriate for non-high-grade and even for some high-grade recurrent tumours [232, 233] (LE: 3). Additionally, there are now several bladder preservation strategies available that can be categorised as intravesical immunotherapy [234], intravesical chemotherapy, device-assisted therapy (see Section 7.2.1.3.2), and combination therapy (see Section 7.2.3) [235]. Changing from BCG to these options can yield responses in selected cases with BCG treatment failure [232, 234-242] (LE: 3).

Treatments other than RC must be considered oncologically inferior in patients with BCG failure at the present time [150, 229, 230] (LE: 3).

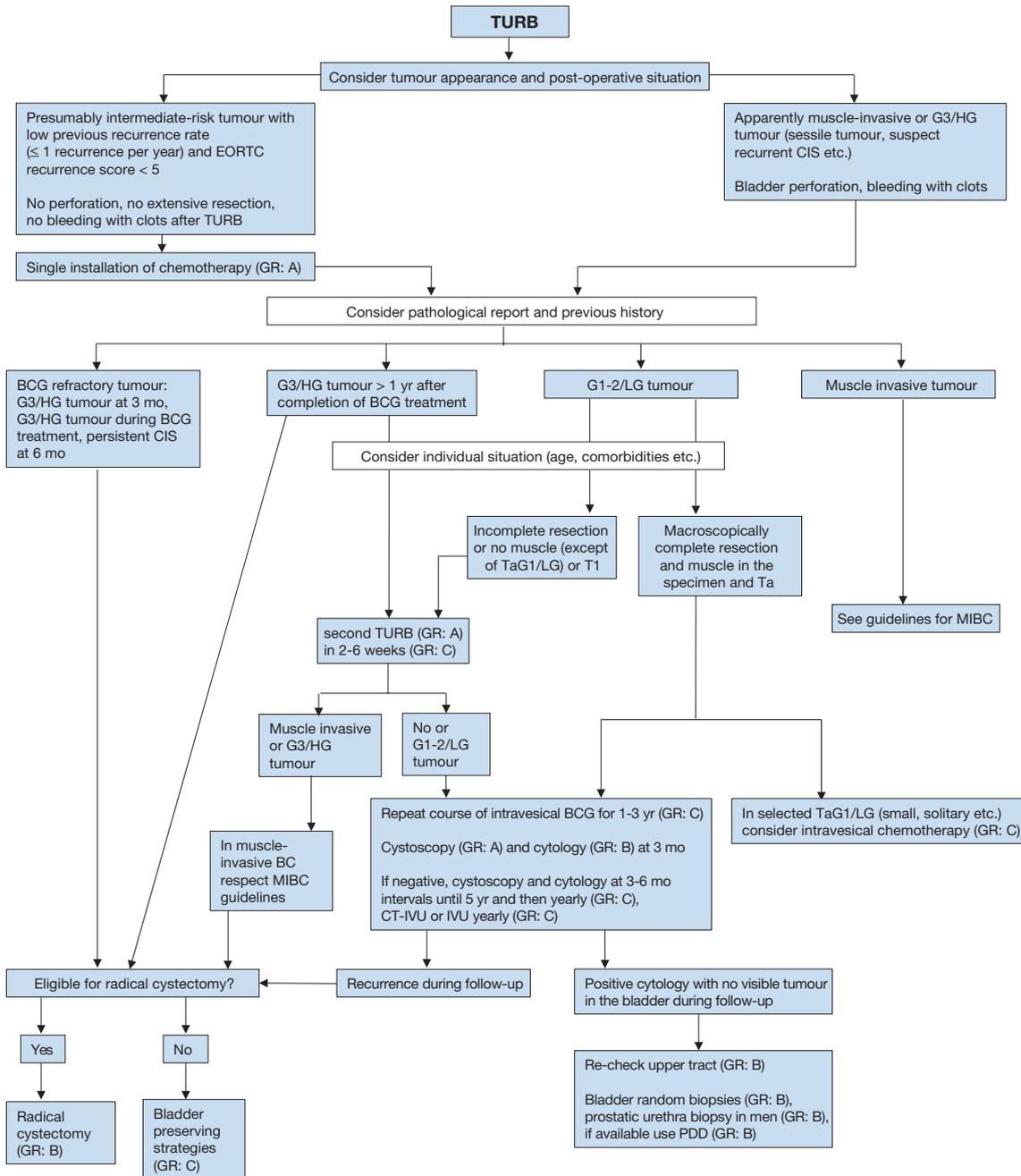
Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

Non-high-grade recurrence after BCG is not considered as BCG failure. Treatment decision should be individualised according to tumour characteristics. It could include chemotherapy or repeat BCG instillations, but the published evidence is very low.

7.3.4 Summary of evidence - treatment failure of intravesical therapy

Summary of evidence	LE
Prior intravesical chemotherapy has no impact on the effect of bacillus Calmette-Guérin (BCG) instillation.	1a
Treatments other than radical cystectomy must be considered oncologically inferior in patients with BCG failure.	3

Flowchart 7.2: Treatment strategy in recurrence during or after intravesical BCG*



BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade; IVU = intravenous urography; LG = low-grade; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.4 Radical cystectomy for NMIBC

If RC is indicated before progression to muscle-invasive tumour, it can be performed as an immediate (immediately after NMIBC diagnosis) or early procedure (after intravesical therapy failure, see Section 7.3).

There are several reasons to consider immediate RC for selected patients with NMIBC:

- The staging accuracy for T1 tumours by TURB is low with 27-51% of patients being upstaged to muscle-invasive tumour at RC [106, 130, 243-246] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).

Patients who experience disease progression to muscle-invasive stage, have a worse prognosis than those who present with 'primary' muscle-invasive disease [247, 248].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life. It is reasonable to propose immediate RC in those patients with NMIBC who are at highest risk of disease

progression (see Section 7.6) [46, 104, 137, 138, 249] (LE: 3).

The benefits and risks of immediate and delayed RC should be discussed with patients, in a shared decision-making process. Individual additional prognostic factors in T1 tumours mentioned in Sections 4.7 and 6.4 should be considered. Early RC is strongly recommended in patients with BCG-refractory tumours, as mentioned above. A delay in RC may lead to decreased disease-specific survival [250] (LE: 3).

In patients in whom RC is performed before progression to MIBC, the five-year disease-free survival rate exceeds 80% [251-253] (LE: 3).

7.5 Recommendations for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

	GR
Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking.	B
The type of further therapy after transurethral resection of the bladder (TURB) should be based on the risk groups shown in Table 6.3 and Section 7.6.	A
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (\leq one recurrence per year) and expected EORTC recurrence score < 5 , one immediate chemotherapy instillation is recommended.	A
In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus three-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	A
In patients with high-risk tumours, full-dose intravesical BCG for one-three years (induction plus three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs and inconveniences.	A
In patients with CIS in the epithelial lining of the prostatic urethra, transurethral resection of the prostate followed by intravesical instillation of BCG can be offered.	C
Discuss immediate radical cystectomy with patients at highest risk of tumour progression (see Section 7.6).	C
Offer radical cystectomy (RC) to patients with BCG failure (see Section 7.7).	B
In patients with BCG failure, who are not candidates for RC due to comorbidities, use preservation strategies (device-assisted instillations of chemotherapy, intravesical chemotherapy, intravesical immunotherapy).	C
Intravesical chemotherapy	
When given, a single immediate instillation of chemotherapy should be administered within 24 hours after TURB, preferably within two hours.	C
A single immediate instillation of chemotherapy should be omitted in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	C
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	C
The optimal schedule of further intravesical chemotherapy instillation and its duration is not defined, it should not exceed one year.	C
If intravesical chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug by reducing fluid intake before and during instillation.	B
The length of individual instillation should be one-two hours.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: <ul style="list-style-type: none"> • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection. 	C
The management of side effects after BCG intravesical instillation should reflect their type and grade (see Table 7.1).	C

7.6 Treatment recommendations in TaT1 tumours and carcinoma *in situ* according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG), < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk).	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either one-year full-dose BCG treatment (induction plus three-weekly instillations at three, six and twelve months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumours	Any of the following: <ul style="list-style-type: none"> • T1 tumours; • G3 (HG) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present). 	Intravesical full-dose BCG instillations for one-three years or radical cystectomy (in highest-risk tumours - <i>see below</i>).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, LVI (see Sections 4.7 and 6.4). BCG failures.	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for one-three years. Radical cystectomy is recommended.

7.7 Treatment recommendations for bacillus Calmette-Guérin (BCG) failure and recurrences after BCG

Category	Treatment recommendation	GR
BCG-refractory tumour	1. Radical cystectomy 2. Bladder-preserving strategies in patients unsuitable for radical cystectomy	B
High-grade (HG) recurrence after BCG	1. Radical cystectomy 2. Bladder-preserving strategies 3. Repeat BCG course	C
Non-HG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy 2. Radical cystectomy	C

8. FOLLOW-UP OF PATIENTS WITH NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need surveillance. However, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk. Using risk tables (see Tables 6.1 and 6.2), the short- and long-term risks of recurrence and progression in individual patients may be predicted and the follow-up schedule adapted accordingly [137, 138].

When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life-threatening.

- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small, TaLG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [254, 255] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden [98] (LE: 3). Some authors have even defended temporary surveillance in selected cases [255-257] (LE: 3).
- The first cystoscopy after TURB at three months is an important prognostic indicator for recurrence and progression [144, 150, 258-260] (LE: 1a). Therefore, the first cystoscopy should always be performed three months after TURB in all patients with TaT1 tumours and CIS.
- In tumours at low risk, the risk of recurrence after five recurrence-free years is low [259] (LE: 3).
- Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered [260].
- In tumours originally intermediate- or high risk, recurrences after ten years tumour-free are not unusual [261] (LE: 3). Therefore, life-long follow-up is recommended [260].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders)
- The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [57] (LE: 3).
- Positive urine test results have a positive impact on the quality of follow-up cystoscopy [83] (LE: 1b) supporting the adjunctive role of urine tests during follow-up.
- In patients initially diagnosed with TaLG/G1-2 BC, ultrasound of the bladder may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [262].

No non-invasive method can replace endoscopy. Follow-up is therefore based on regular cystoscopy (see Section 5.7). There is a lack of randomised studies investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

As CIS is often not visible, multiple biopsies may be necessary in selected cases to confirm the efficacy of intravesical treatment in patients treated for CIS [84]. The recommendations for follow-up are mainly based on retrospective data (see Section 8.1).

8.1 Summary of evidence and recommendations for follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer

Summary of evidence	LE
The first cystoscopy after transurethral resection of the bladder at 3 months is an important prognostic indicator for recurrence and progression.	1a
The risk of upper urinary tract (UUT) recurrence increases in patients with multiple- and high-risk tumours.	3

Recommendations	GR
Base follow-up of TaT1 tumours and carcinoma <i>in situ</i> (CIS) on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then yearly.	C
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy and cytology.	C
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk tumours.	C
Endoscopy under anaesthesia and bladder biopsies should be performed when office cystoscopy shows suspicious findings or if urinary cytology is positive.	B
Consider random (R)-biopsies or photodynamic diagnosis (PDD)-guided biopsies after intravesical treatment (at three or six months) in patients with CIS.	C
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B
In patients initially diagnosed with TaLG/G1-2 bladder cancer, use ultrasound of the bladder during surveillance in case cystoscopy is not possible or refused by the patient.	C

9. REFERENCES

1. Rouprêt, M., *et al.* Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma. EAU Guidelines 2017. Edn presented at the 32nd EAU Annual Congress London.
2. Witjes, J., *et al.* EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. EAU Guidelines 2017. Edn presented at the 32nd EAU Annual Congress London.
3. Gakis, G., *et al.* Guidelines on Primary Urethral Carcinoma. EAU Guidelines 2017. Edn presented at the 32nd EAU Annual Congress London.
4. Babjuk, M., *et al.* EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. *Eur Urol*, 2016. 71: 447.
<https://www.ncbi.nlm.nih.gov/pubmed/27324428>
5. Phillips, B. Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
6. Hernandez, V., *et al.* Is there a difference between the 2004 WHO grading system and the 1973 WHO grading system for NMIBC in terms of prognostic performance?. PROSPERO International prospective register of systematic reviews, 2015.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015025045
7. Ferlay J., *et al.* GLOBOCAN 2012 v1.0: Estimated cancer incidence, mortality and prevalence worldwide in 2012. 2013. 2015.
<http://globocan.iarc.fr/Default.aspx>
8. Burger, M., *et al.* Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*, 2013. 63: 234.
<https://www.ncbi.nlm.nih.gov/pubmed/22877502>
9. Chavan, S., *et al.* International variations in bladder cancer incidence and mortality. *Eur Urol*, 2014. 66: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/24451595>
10. Comperat, E., *et al.* Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. *Virchows Arch*, 2015. 466: 589.
<https://www.ncbi.nlm.nih.gov/pubmed/25697540>
11. Freedman, N.D., *et al.* Association between smoking and risk of bladder cancer among men and women. *JAMA*, 2011. 306: 737.
<https://www.ncbi.nlm.nih.gov/pubmed/21846855>
12. Colt, J.S., *et al.* A case-control study of occupational exposure to metalworking fluids and bladder cancer risk among men. *Occup Environ Med*, 2014. 71: 667.
<https://www.ncbi.nlm.nih.gov/pubmed/25201311>
13. Pesch, B., *et al.* Screening for bladder cancer with urinary tumor markers in chemical workers with exposure to aromatic amines. *Int Arch Occup Environ Health*, 2013.
<https://www.ncbi.nlm.nih.gov/pubmed/24129706>
14. Egbers, L., *et al.* The prognostic value of family history among patients with urinary bladder cancer. *Int J Cancer*, 2015. 136: 1117.
<https://www.ncbi.nlm.nih.gov/pubmed/24978702>
15. Corral, R., *et al.* Comprehensive analyses of DNA repair pathways, smoking and bladder cancer risk in Los Angeles and Shanghai. *Int J Cancer*, 2014. 135: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/24382701>
16. Figueroa, J.D., *et al.* Identification of a novel susceptibility locus at 13q34 and refinement of the 20p12.2 region as a multi-signal locus associated with bladder cancer risk in individuals of European ancestry. *Hum Mol Genet*, 2016. 25: 1203.
<https://www.ncbi.nlm.nih.gov/pubmed/26732427>
17. Steinmaus, C., *et al.* Increased lung and bladder cancer incidence in adults after in utero and early-life arsenic exposure. *Cancer Epidemiol Biomarkers Prev*, 2014. 23: 1529.
<https://www.ncbi.nlm.nih.gov/pubmed/24859871>
18. Buckland, G., *et al.* Adherence to the Mediterranean diet and risk of bladder cancer in the EPIC cohort study. *Int J Cancer*, 2014. 134: 2504.
<https://www.ncbi.nlm.nih.gov/pubmed/24226765>
19. Liu, H., *et al.* Fruit and vegetable consumption and risk of bladder cancer: an updated meta-analysis of observational studies. *Eur J Cancer Prev*, 2015. 24: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/25642791>

20. Vieira, A.R., *et al.* Fruits, vegetables, and bladder cancer risk: a systematic review and meta-analysis. *Cancer Med*, 2015. 4: 136.
<https://www.ncbi.nlm.nih.gov/pubmed/25461441>
21. TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. Brierley JD, Gospodarowicz M, Wittekind C (Eds). 2017, Wiley-Blackwell.
<http://www.uicc.org/resources/tnm/publications-resources>
22. Orsola, A., *et al.* Initial high-grade T1 urothelial cell carcinoma: feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. *Eur Urol*, 2005. 48: 231.
<https://www.ncbi.nlm.nih.gov/pubmed/15963635>
23. van Rhijn, B.W., *et al.* A new and highly prognostic system to discern T1 bladder cancer substage. *Eur Urol*, 2012. 61: 378.
<https://www.ncbi.nlm.nih.gov/pubmed/22036775>
24. Moch, H., *et al.*, WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed. ed, ed. O. H. 2016, Lyon, France
<http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=70&codcch=4008>
25. Sauter G, A.F., *et al.*, Tumours of the urinary system: non-invasive urothelial neoplasias. In: WHO classification of classification of tumours of the urinary system and male genital organs., 2004, IARCC Press: Lyon.
<http://publications.iarc.fr/Book-And-Report-Series/Who-Iarc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organs-2016>
26. Epstein, J.I., *et al.* The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol*, 1998. 22: 1435.
<https://www.ncbi.nlm.nih.gov/pubmed/9850170>
27. van Rhijn, B.W., *et al.* The pathologist's mean grade is constant and individualizes the prognostic value of bladder cancer grading. *Eur Urol*, 2010. 57: 1052.
<https://www.ncbi.nlm.nih.gov/pubmed/19765886>
28. May, M., *et al.* Prognostic accuracy of individual uropathologists in noninvasive urinary bladder carcinoma: a multicentre study comparing the 1973 and 2004 World Health Organisation classifications. *Eur Urol*, 2010. 57: 850.
<https://www.ncbi.nlm.nih.gov/pubmed/19346063>
29. Otto, W., *et al.* The WHO classification of 1973 is more suitable than the WHO classification of 2004 for predicting survival in pT1 urothelial bladder cancer. *BJU Int*, 2011. 107: 404.
<https://www.ncbi.nlm.nih.gov/pubmed/20707791>
30. MacLennan, G.T., *et al.* Histologic grading of noninvasive papillary urothelial neoplasms. *Eur Urol*, 2007. 51: 889.
<https://www.ncbi.nlm.nih.gov/pubmed/17095142>
31. Sylvester, R.J., *et al.* High-grade Ta urothelial carcinoma and carcinoma *in situ* of the bladder. *Urology*, 2005. 66: 90.
<https://www.ncbi.nlm.nih.gov/pubmed/16399418>
32. Lamm, D., *et al.* Updated concepts and treatment of carcinoma *in situ*. *Urol Oncol*, 1998. 4: 130.
<https://www.ncbi.nlm.nih.gov/pubmed/21227218>
33. Witjes, J.A., *et al.* Review pathology in a diagnostic bladder cancer trial: effect of patient risk category. *Urology*, 2006. 67: 751.
<https://www.ncbi.nlm.nih.gov/pubmed/16566990>
34. van Rhijn, B.W., *et al.* Pathological stage review is indicated in primary pT1 bladder cancer. *BJU Int*, 2010. 106: 206.
<https://www.ncbi.nlm.nih.gov/pubmed/20002439>
35. Comperat, E., *et al.* An interobserver reproducibility study on invasiveness of bladder cancer using virtual microscopy and heatmaps. *Histopathology*, 2013. 63: 756.
<https://www.ncbi.nlm.nih.gov/pubmed/24102813>
36. Mangrud, O.M., *et al.* Reproducibility and prognostic value of WHO1973 and WHO2004 grading systems in TaT1 urothelial carcinoma of the urinary bladder. *PLoS One*, 2014. 9: e83192.
<https://www.ncbi.nlm.nih.gov/pubmed/24409280>
37. Luchey, A.M., *et al.* Change in Management Based on Pathologic Second Opinion Among Bladder Cancer Patients Presenting to a Comprehensive Cancer Center: Implications for Clinical Practice. *Urology*, 2016. 93: 130.
<https://www.ncbi.nlm.nih.gov/pubmed/27041469>

38. Cho, K.S., *et al.* Lymphovascular invasion in transurethral resection specimens as predictor of progression and metastasis in patients with newly diagnosed T1 bladder urothelial cancer. *J Urol*, 2009. 182: 2625.
<https://www.ncbi.nlm.nih.gov/pubmed/19836779>
39. Comperat, E., *et al.* Micropapillary urothelial carcinoma of the urinary bladder: a clinicopathological analysis of 72 cases. *Pathology*, 2010. 42: 650.
<https://www.ncbi.nlm.nih.gov/pubmed/21080874>
40. Kaimakliotis, H.Z., *et al.* Plasmacytoid variant urothelial bladder cancer: is it time to update the treatment paradigm? *Urol Oncol*, 2014. 32: 833.
<https://www.ncbi.nlm.nih.gov/pubmed/24954925>
41. Willis, D.L., *et al.* Micropapillary bladder cancer: current treatment patterns and review of the literature. *Urol Oncol*, 2014. 32: 826.
<https://www.ncbi.nlm.nih.gov/pubmed/24931270>
42. Beltran, A.L., *et al.* Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder. *Virchows Arch*, 2014. 465: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/24878757>
43. Soave, A., *et al.* Does the extent of variant histology affect oncological outcomes in patients with urothelial carcinoma of the bladder treated with radical cystectomy? *Urol Oncol*, 2015. 33: 21 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/25465301>
44. Masson-Lecomte, A., *et al.* Oncological outcomes of advanced muscle-invasive bladder cancer with a micropapillary variant after radical cystectomy and adjuvant platinum-based chemotherapy. *World J Urol*, 2015. 33: 1087.
<https://www.ncbi.nlm.nih.gov/pubmed/25179011>
45. Seisen, T., *et al.* Impact of histological variants on the outcomes of nonmuscle invasive bladder cancer after transurethral resection. *Curr Opin Urol*, 2014. 24: 524.
<https://www.ncbi.nlm.nih.gov/pubmed/25051021>
46. Willis, D.L., *et al.* Clinical outcomes of cT1 micropapillary bladder cancer. *J Urol*, 2015. 193: 1129.
<https://www.ncbi.nlm.nih.gov/pubmed/25254936>
47. Burger, M., *et al.* Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. *Eur Urol*, 2008. 54: 835.
<https://www.ncbi.nlm.nih.gov/pubmed/18166262>
48. Frstrup, N., *et al.* Cathepsin E, maspin, Plk1, and survivin are promising prognostic protein markers for progression in non-muscle invasive bladder cancer. *Am J Pathol*, 2012. 180: 1824.
<https://www.ncbi.nlm.nih.gov/pubmed/22449953>
49. Palou, J., *et al.* Protein expression patterns of ezrin are predictors of progression in T1G3 bladder tumours treated with nonmaintenance bacillus Calmette-Guerin. *Eur Urol*, 2009. 56: 829.
<https://www.ncbi.nlm.nih.gov/pubmed/18926620>
50. van Rhijn, B.W., *et al.* The FGFR3 mutation is related to favorable pT1 bladder cancer. *J Urol*, 2012. 187: 310.
<https://www.ncbi.nlm.nih.gov/pubmed/22099989>
51. Remy, E., *et al.* A Modeling Approach to Explain Mutually Exclusive and Co-Occurring Genetic Alterations in Bladder Tumorigenesis. *Cancer Res*, 2015. 75: 4042.
<https://www.ncbi.nlm.nih.gov/pubmed/26238783>
52. Ramirez, D., *et al.* Microscopic haematuria at time of diagnosis is associated with lower disease stage in patients with newly diagnosed bladder cancer. *BJU Int*, 2016. 117: 783.
<https://www.ncbi.nlm.nih.gov/pubmed/26435378>
53. Nolte-Ernsting, C., *et al.* Understanding multislice CT urography techniques: Many roads lead to Rome. *Eur Radiol*, 2006. 16: 2670.
<https://www.ncbi.nlm.nih.gov/pubmed/16953373>
54. Goessel, C., *et al.* Is routine excretory urography necessary at first diagnosis of bladder cancer? *J Urol*, 1997. 157: 480.
<https://www.ncbi.nlm.nih.gov/pubmed/8996338>
55. Palou, J., *et al.* Multivariate analysis of clinical parameters of synchronous primary superficial bladder cancer and upper urinary tract tumor. *J Urol*, 2005. 174: 859.
<https://www.ncbi.nlm.nih.gov/pubmed/16093970>
56. Holmang, S., *et al.* Long-term followup of a bladder carcinoma cohort: routine followup urography is not necessary. *J Urol*, 1998. 160: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/9628602>

57. Millan-Rodriguez, F., *et al.* Upper urinary tract tumors after primary superficial bladder tumors: prognostic factors and risk groups. *J Urol*, 2000. 164: 1183.
<https://www.ncbi.nlm.nih.gov/pubmed/10992362>
58. Hilton, S., *et al.* Recent advances in imaging cancer of the kidney and urinary tract. *Surg Oncol Clin N Am*, 2014. 23: 863.
<https://www.ncbi.nlm.nih.gov/pubmed/25246053>
59. Yafi, F.A., *et al.* Prospective analysis of sensitivity and specificity of urinary cytology and other urinary biomarkers for bladder cancer. *Urol Oncol*, 2015. 33: 66 e25.
<https://www.ncbi.nlm.nih.gov/pubmed/25037483>
60. Tetu, B. Diagnosis of urothelial carcinoma from urine. *Mod Pathol*, 2009. 22 Suppl 2: S53.
<https://www.ncbi.nlm.nih.gov/pubmed/19494853>
61. Raitanen, M.P., *et al.* Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. *Eur Urol*, 2002. 41: 284.
<https://www.ncbi.nlm.nih.gov/pubmed/12180229>
62. Rosenthal DL., *et al.*, The Paris System for Reporting Urinary Cytology. 2016, Switzerland.
<http://www.springer.com/us/book/9783319228631>
63. Burton, J.L., *et al.* Demand management in urine cytology: a single cytospin slide is sufficient. *J Clin Pathol*, 2000. 53: 718.
<https://www.ncbi.nlm.nih.gov/pubmed/11041065>
64. Nabi, G., *et al.* Suspicious urinary cytology with negative evaluation for malignancy in the diagnostic investigation of haematuria: how to follow up? *J Clin Pathol*, 2004. 57: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/15047737>
65. Lokeshwar, V.B., *et al.* Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. *Urology*, 2005. 66: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/16399415>
66. Glas, A.S., *et al.* Tumor markers in the diagnosis of primary bladder cancer. A systematic review. *J Urol*, 2003. 169: 1975.
<https://www.ncbi.nlm.nih.gov/pubmed/12771702>
67. van Rhijn, B.W., *et al.* Urine markers for bladder cancer surveillance: a systematic review. *Eur Urol*, 2005. 47: 736.
<https://www.ncbi.nlm.nih.gov/pubmed/15925067>
68. Lotan, Y., *et al.* Considerations on implementing diagnostic markers into clinical decision making in bladder cancer. *Urol Oncol*, 2010. 28: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/20610281>
69. Yutkin, V., *et al.* Can urinary biomarkers replace cystoscopic examination in bladder cancer surveillance? *Expert Rev Anticancer Ther*, 2010. 10: 787.
<https://www.ncbi.nlm.nih.gov/pubmed/20553203>
70. Hajdinjak, T. UroVysion FISH test for detecting urothelial cancers: meta-analysis of diagnostic accuracy and comparison with urinary cytology testing. *Urol Oncol*, 2008. 26: 646.
<https://www.ncbi.nlm.nih.gov/pubmed/18367109>
71. Schlomer, B.J., *et al.* Prospective validation of the clinical usefulness of reflex fluorescence *in situ* hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. *J Urol*, 2010. 183: 62.
<https://www.ncbi.nlm.nih.gov/pubmed/19913822>
72. Kamat, A.M., *et al.* Prospective trial to identify optimal bladder cancer surveillance protocol: reducing costs while maximizing sensitivity. *BJU Int*, 2011. 108: 1119.
<https://www.ncbi.nlm.nih.gov/pubmed/21426474>
73. Vrooman, O.P., *et al.* Urinary markers in bladder cancer. *Eur Urol*, 2008. 53: 909.
<https://www.ncbi.nlm.nih.gov/pubmed/18162285>
74. Todenhofer, T., *et al.* Prognostic relevance of positive urine markers in patients with negative cystoscopy during surveillance of bladder cancer. *BMC Cancer*, 2015. 15: 155.
<https://www.ncbi.nlm.nih.gov/pubmed/25884545>
75. van der Aa, M.N., *et al.* Microsatellite analysis of voided-urine samples for surveillance of low-grade non-muscle-invasive urothelial carcinoma: feasibility and clinical utility in a prospective multicenter study (Cost-Effectiveness of Follow-Up of Urinary Bladder Cancer trial [CEFUB]). *Eur Urol*, 2009. 55: 659.
<https://www.ncbi.nlm.nih.gov/pubmed/25884545>

76. Roupret, M., *et al.* A comparison of the performance of microsatellite and methylation urine analysis for predicting the recurrence of urothelial cell carcinoma, and definition of a set of markers by Bayesian network analysis. *BJU Int*, 2008. 101: 1448.
<https://www.ncbi.nlm.nih.gov/pubmed/18325051>
77. Grossman, H.B., *et al.* Detection of bladder cancer using a point-of-care proteomic assay. *JAMA*, 2005. 293: 810.
<https://www.ncbi.nlm.nih.gov/pubmed/15713770>
78. Kim, P.H., *et al.* Reflex fluorescence *in situ* hybridization assay for suspicious urinary cytology in patients with bladder cancer with negative surveillance cystoscopy. *BJU Int*, 2014. 114: 354.
<https://www.ncbi.nlm.nih.gov/pubmed/24128299>
79. Roobol, M.J., *et al.* Feasibility study of screening for bladder cancer with urinary molecular markers (the BLU-P project). *Urol Oncol*, 2010. 28: 686.
<https://www.ncbi.nlm.nih.gov/pubmed/21062653>
80. Lotan, Y., *et al.* Should we screen for bladder cancer in a high-risk population?: A cost per life-year saved analysis. *Cancer*, 2006. 107: 982.
<https://www.ncbi.nlm.nih.gov/pubmed/16862567>
81. Grossman, H.B., *et al.* Surveillance for recurrent bladder cancer using a point-of-care proteomic assay. *JAMA*, 2006. 295: 299.
<https://www.ncbi.nlm.nih.gov/pubmed/16418465>
82. Babjuk, M., *et al.* Urinary cytology and quantitative BTA and UBC tests in surveillance of patients with pT1 bladder urothelial carcinoma. *Urology*, 2008. 71: 718.
<https://www.ncbi.nlm.nih.gov/pubmed/18387400>
83. van der Aa, M.N., *et al.* Cystoscopy revisited as the gold standard for detecting bladder cancer recurrence: diagnostic review bias in the randomized, prospective CEFUB trial. *J Urol*, 2010. 183: 76.
<https://www.ncbi.nlm.nih.gov/pubmed/19913254>
84. Kurth, K.H., *et al.* Current methods of assessing and treating carcinoma *in situ* of the bladder with or without involvement of the prostatic urethra. *Int J Urol*, 1995. 2 Suppl 2: 8.
<https://www.ncbi.nlm.nih.gov/pubmed/7553309>
85. Aaronson, D.S., *et al.* Meta-analysis: does lidocaine gel before flexible cystoscopy provide pain relief? *BJU Int*, 2009. 104: 506.
<https://www.ncbi.nlm.nih.gov/pubmed/19239453>
86. Brausi, M., *et al.* Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. *Eur Urol*, 2002. 41: 523.
<https://www.ncbi.nlm.nih.gov/pubmed/12074794>
87. Richterstetter, M., *et al.* The value of extended transurethral resection of bladder tumour (TURBT) in the treatment of bladder cancer. *BJU Int*, 2012. 110: E76.
<https://www.ncbi.nlm.nih.gov/pubmed/22313727>
88. Kramer, M.W., *et al.* En bloc resection of urothelium carcinoma of the bladder (EBRUC): a European multicenter study to compare safety, efficacy, and outcome of laser and electrical en bloc transurethral resection of bladder tumor. *World J Urol*, 2015. 33: 1937.
<https://www.ncbi.nlm.nih.gov/pubmed/25910478>
89. Hurle, R., *et al.* "En Bloc" Resection of Nonmuscle Invasive Bladder Cancer: A Prospective Single-center Study. *Urology*, 2016. 90: 126.
<https://www.ncbi.nlm.nih.gov/pubmed/26776561>
90. Migliari, R., *et al.* Thulium Laser Endoscopic En Bloc Enucleation of Nonmuscle-Invasive Bladder Cancer. *J Endourol*, 2015. 29: 1258.
<https://www.ncbi.nlm.nih.gov/pubmed/26102556>
91. Zhang, X.R., *et al.* Two Micrometer Continuous-Wave Thulium Laser Treating Primary Non-Muscle-Invasive Bladder Cancer: Is It Feasible? A Randomized Prospective Study. *Photomed Laser Surg*, 2015. 33: 517.
<https://www.ncbi.nlm.nih.gov/pubmed/26397029>
92. Mariappan, P., *et al.* Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. *Eur Urol*, 2010. 57: 843.
<https://www.ncbi.nlm.nih.gov/pubmed/19524354>

93. Mariappan, P., *et al.* Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking. *BJU Int*, 2012. 109: 1666.
<https://www.ncbi.nlm.nih.gov/pubmed/22044434>
94. Gupta, N.P., *et al.* Bipolar energy for transurethral resection of bladder tumours at low-power settings: initial experience. *BJU Int*, 2011. 108: 553.
<https://www.ncbi.nlm.nih.gov/pubmed/21176081>
95. Venkatramani, V., *et al.* Monopolar versus bipolar transurethral resection of bladder tumors: a single center, parallel arm, randomized, controlled trial. *J Urol*, 2014. 191: 1703.
<https://www.ncbi.nlm.nih.gov/pubmed/24333244>
96. Sugihara, T., *et al.* Comparison of Perioperative Outcomes including Severe Bladder Injury between Monopolar and Bipolar Transurethral Resection of Bladder Tumors: A Population Based Comparison. *J Urol*, 2014. 192: 1355.
<https://www.ncbi.nlm.nih.gov/pubmed/24893311>
97. Mashni, J., *et al.* Prospective evaluation of plasma kinetic bipolar resection of bladder cancer: comparison to monopolar resection and pathologic findings. *Int Urol Nephrol*, 2014. 46: 1699.
<https://www.ncbi.nlm.nih.gov/pubmed/24792236>
98. Herr, H.W., *et al.* Management of low grade papillary bladder tumors. *J Urol*, 2007. 178: 1201.
<https://www.ncbi.nlm.nih.gov/pubmed/17698090>
99. Xu, Y., *et al.* Comparing the treatment outcomes of potassium-titanyl-phosphate laser vaporization and transurethral electroresection for primary nonmuscle-invasive bladder cancer: A prospective, randomized study. *Lasers Surg Med*, 2015. 47: 306.
<https://www.ncbi.nlm.nih.gov/pubmed/25864416>
100. Picozzi, S.C., *et al.* Is it oncologically safe performing simultaneous transurethral resection of the bladder and prostate? A meta-analysis on 1,234 patients. *Int Urol Nephrol*, 2012. 44: 1325.
<https://www.ncbi.nlm.nih.gov/pubmed/22710969>
101. Tsivian, A., *et al.* Simultaneous transurethral resection of bladder tumor and benign prostatic hyperplasia: hazardous or a safe timesaver? *J Urol*, 2003. 170: 2241.
<https://www.ncbi.nlm.nih.gov/pubmed/14634388>
102. van der Meijden, A., *et al.* Significance of bladder biopsies in Ta,T1 bladder tumors: a report from the EORTC Genito-Urinary Tract Cancer Cooperative Group. EORTC-GU Group Superficial Bladder Committee. *Eur Urol*, 1999. 35: 267.
<https://www.ncbi.nlm.nih.gov/pubmed/10419345>
103. Hara, T., *et al.* Risk of concomitant carcinoma *in situ* determining biopsy candidates among primary non-muscle-invasive bladder cancer patients: retrospective analysis of 173 Japanese cases. *Int J Urol*, 2009. 16: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/19207607>
104. Palou, J., *et al.* Female gender and carcinoma *in situ* in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guerin. *Eur Urol*, 2012. 62: 118.
<https://www.ncbi.nlm.nih.gov/pubmed/22101115>
105. Mungan, M.U., *et al.* Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. *Eur Urol*, 2005. 48: 760.
<https://www.ncbi.nlm.nih.gov/pubmed/16005563>
106. Huguet, J., *et al.* Cystectomy in patients with high risk superficial bladder tumors who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. *Eur Urol*, 2005. 48: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/15967252>
107. Kausch, I., *et al.* Photodynamic diagnosis in non-muscle-invasive bladder cancer: a systematic review and cumulative analysis of prospective studies. *Eur Urol*, 2010. 57: 595.
<https://www.ncbi.nlm.nih.gov/pubmed/20004052>
108. Mowatt, G., *et al.* Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: Systematic review and meta-analysis. *Int J Technol Assess Health Care*, 2011. 27: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/21262078>
109. Neuzillet, Y., *et al.* Assessment of diagnostic gain with hexaminolevulinatate (HAL) in the setting of newly diagnosed non-muscle-invasive bladder cancer with positive results on urine cytology. *Urol Oncol*, 2014. 32: 1135.
<https://www.ncbi.nlm.nih.gov/pubmed/25023786>

110. Draga, R.O., *et al.* Photodynamic diagnosis (5-aminolevulinic acid) of transitional cell carcinoma after bacillus Calmette-Guerin immunotherapy and mitomycin C intravesical therapy. *Eur Urol*, 2010. 57: 655.
<https://www.ncbi.nlm.nih.gov/pubmed/19819064>
111. Ray, E.R., *et al.* Hexylaminolevulinatate fluorescence cystoscopy in patients previously treated with intravesical bacille Calmette-Guerin. *BJU Int*, 2010. 105: 789.
<https://www.ncbi.nlm.nih.gov/pubmed/19832725>
112. Schumacher, M.C., *et al.* Transurethral resection of non-muscle-invasive bladder transitional cell cancers with or without 5-aminolevulinic Acid under visible and fluorescent light: results of a prospective, randomised, multicentre study. *Eur Urol*, 2010. 57: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/19913351>
113. Stenzl, A., *et al.* Detection and clinical outcome of urinary bladder cancer with 5-aminolevulinic acid-induced fluorescence cystoscopy : A multicenter randomized, double-blind, placebo-controlled trial. *Cancer*, 2011. 117: 938.
<https://www.ncbi.nlm.nih.gov/pubmed/21351082>
114. Burger, M., *et al.* Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinatate cystoscopy: a meta-analysis of detection and recurrence based on raw data. *Eur Urol*, 2013. 64: 846.
<https://www.ncbi.nlm.nih.gov/pubmed/23602406>
115. O'Brien, T., *et al.* Prospective randomized trial of hexylaminolevulinatate photodynamic-assisted transurethral resection of bladder tumour (TURBT) plus single-shot intravesical mitomycin C vs conventional white-light TURBT plus mitomycin C in newly presenting non-muscle-invasive bladder cancer. *BJU Int*, 2013. 112: 1096.
<https://www.ncbi.nlm.nih.gov/pubmed/24053153>
116. Gkritisios, P., *et al.* Hexaminolevulinatate-guided transurethral resection of non-muscle-invasive bladder cancer does not reduce the recurrence rates after a 2-year follow-up: a prospective randomized trial. *Int Urol Nephrol*, 2014. 46: 927.
<https://www.ncbi.nlm.nih.gov/pubmed/24249423>
117. Mariappan, P., *et al.* Real-life Experience: Early Recurrence With Hexvix Photodynamic Diagnosis-assisted Transurethral Resection of Bladder Tumour vs Good-quality White Light TURBT in New Non-muscle-invasive Bladder Cancer. *Urology*, 2015. 86: 327.
<https://www.ncbi.nlm.nih.gov/pubmed/26142924>
118. Cauberg, E.C., *et al.* Narrow band imaging cystoscopy improves the detection of non-muscle-invasive bladder cancer. *Urology*, 2010. 76: 658.
<https://www.ncbi.nlm.nih.gov/pubmed/20223505>
119. Zheng, C., *et al.* Narrow band imaging diagnosis of bladder cancer: systematic review and meta-analysis. *BJU Int*, 2012. 110: E680.
<https://www.ncbi.nlm.nih.gov/pubmed/22985502>
120. Naito, S., *et al.* The Clinical Research Office of the Endourological Society (CROES) Multicentre Randomised Trial of Narrow Band Imaging-Assisted Transurethral Resection of Bladder Tumour (TURBT) Versus Conventional White Light Imaging-Assisted TURBT in Primary Non-Muscle-invasive Bladder Cancer Patients: Trial Protocol and 1-year Results. *Eur Urol*, 2016. 70: 506.
<https://www.ncbi.nlm.nih.gov/pubmed/27117749>
121. Grimm, M.O., *et al.* Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol*, 2003. 170: 433.
<https://www.ncbi.nlm.nih.gov/pubmed/12853793>
122. Divrik, R.T., *et al.* The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. *J Urol*, 2006. 175: 1641.
<https://www.ncbi.nlm.nih.gov/pubmed/16600720>
123. Lazica, D.A., *et al.* Second transurethral resection after Ta high-grade bladder tumor: a 4.5-year period at a single university center. *Urol Int*, 2014. 92: 131.
<https://www.ncbi.nlm.nih.gov/pubmed/23988813>
124. Vasdev, N., *et al.* The impact of early re-resection in patients with pT1 high-grade non-muscle invasive bladder cancer. *Ecancermedalscience*, 2012. 6: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/22988482>
125. Angulo, J.C., *et al.* Second transurethral resection and prognosis of high-grade non-muscle invasive bladder cancer in patients not receiving bacillus Calmette-Guerin. *Actas Urol Esp*, 2014. 38: 164.
<https://www.ncbi.nlm.nih.gov/pubmed/24613147>

126. Gendy, R., *et al.* Repeat transurethral resection for non-muscle-invasive bladder cancer: a contemporary series. *BJU Int*, 2016. 117 Suppl 4: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/26486968>
127. Hashine, K., *et al.* Results of second transurethral resection for high-grade T1 bladder cancer. *Urol Ann*, 2016. 8: 10.
<https://www.ncbi.nlm.nih.gov/pubmed/26834394>
128. El-Barky, E., *et al.* The importance of second-look transurethral resection for superficial bladder cancer. *J Clin Urol*, 2015. 8: 299.
<http://journals.sagepub.com/doi/pdf/10.1177/2051415814560189>
129. Dalbagni, G., *et al.* Clinical outcome in a contemporary series of restaged patients with clinical T1 bladder cancer. *Eur Urol*, 2009. 56: 903.
<https://www.ncbi.nlm.nih.gov/pubmed/19632765>
130. Fritsche, H.M., *et al.* Characteristics and outcomes of patients with clinical T1 grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. *Eur Urol*, 2010. 57: 300.
<https://www.ncbi.nlm.nih.gov/pubmed/19766384>
131. Kulkarni, G.S., *et al.* An updated critical analysis of the treatment strategy for newly diagnosed high-grade T1 (previously T1G3) bladder cancer. *Eur Urol*, 2010. 57: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/19740595>
132. Sfakianos, J.P., *et al.* The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette-Guerin. *J Urol*, 2014. 191: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/23973518>
133. Bishr, M., *et al.* Tumour stage on re-staging transurethral resection predicts recurrence and progression-free survival of patients with high-risk non-muscle invasive bladder cancer. *Can Urol Assoc J*, 2014. 8: E306.
<https://www.ncbi.nlm.nih.gov/pubmed/24940455>
134. Gontero, P., *et al.* The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette-Guerin. *BJU Int*, 2016. 118: 44.
<https://www.ncbi.nlm.nih.gov/pubmed/26469362>
135. Baltaci, S., *et al.* Significance of the interval between first and second transurethral resection on recurrence and progression rates in patients with high-risk non-muscle-invasive bladder cancer treated with maintenance intravesical Bacillus Calmette-Guerin. *BJU Int*, 2015. 116: 721.
<https://www.ncbi.nlm.nih.gov/pubmed/25715815>
136. Lopez-Beltran, A., *et al.* Handling and pathology reporting of specimens with carcinoma of the urinary bladder, ureter, and renal pelvis. *Eur Urol*, 2004. 45: 257.
<https://www.ncbi.nlm.nih.gov/pubmed/15036668>
137. Sylvester, R.J., *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol*, 2006. 49: 466.
<https://www.ncbi.nlm.nih.gov/pubmed/16442208>
138. Fernandez-Gomez, J., *et al.* Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. *J Urol*, 2009. 182: 2195.
<https://www.ncbi.nlm.nih.gov/pubmed/19758621>
139. van Rhijn, B.W., *et al.* Molecular grade (FGFR3/MIB-1) and EORTC risk scores are predictive in primary non-muscle-invasive bladder cancer. *Eur Urol*, 2010. 58: 433.
<https://www.ncbi.nlm.nih.gov/pubmed/20646825>
140. Fernandez-Gomez, J., *et al.* The EORTC tables overestimate the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: external validation of the EORTC risk tables. *Eur Urol*, 2011. 60: 423.
<https://www.ncbi.nlm.nih.gov/pubmed/21621906>
141. Cambier, S., *et al.* EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. *Eur Urol*, 2016. 69: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/26210894>

142. Gontero, P., *et al.* Prognostic factors and risk groups in T1G3 non-muscle-invasive bladder cancer patients initially treated with Bacillus Calmette-Guerin: results of a retrospective multicenter study of 2451 patients. *Eur Urol*, 2015. 67: 74.
<https://www.ncbi.nlm.nih.gov/pubmed/25043942>
143. Golijanin, D., *et al.* Carcinoma in a bladder diverticulum: presentation and treatment outcome. *J Urol*, 2003. 170: 1761.
<https://www.ncbi.nlm.nih.gov/pubmed/14532771>
144. Palou, J., *et al.* Recurrence at three months and high-grade recurrence as prognostic factor of progression in multivariate analysis of T1G2 bladder tumors. *Urology*, 2009. 73: 1313.
<https://www.ncbi.nlm.nih.gov/pubmed/19362341>
145. Alkhateeb, S.S., *et al.* Long-term prognostic value of the combination of EORTC risk group calculator and molecular markers in non-muscle-invasive bladder cancer patients treated with intravesical Bacille Calmette-Guerin. *Urol Ann*, 2011. 3: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/21976923>
146. Lamm, D.L. Carcinoma *in situ*. *Urol Clin North Am*, 1992. 19: 499.
<https://www.ncbi.nlm.nih.gov/pubmed/1636234>
147. Losa, A., *et al.* Low dose bacillus Calmette-Guerin for carcinoma *in situ* of the bladder: long-term results. *J Urol*, 2000. 163: 68.
<https://www.ncbi.nlm.nih.gov/pubmed/10604316>
148. Griffiths, T.R., *et al.* Treatment of carcinoma *in situ* with intravesical bacillus Calmette-Guerin without maintenance. *J Urol*, 2002. 167: 2408.
<https://www.ncbi.nlm.nih.gov/pubmed/11992047>
149. Takenaka, A., *et al.* Clinical outcomes of bacillus Calmette-Guerin instillation therapy for carcinoma *in situ* of urinary bladder. *Int J Urol*, 2008. 15: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/18380817>
150. Solsona, E., *et al.* The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. *J Urol*, 2000. 164: 685.
<https://www.ncbi.nlm.nih.gov/pubmed/10953125>
151. van Gils-Gielen, R.J., *et al.* Risk factors in carcinoma *in situ* of the urinary bladder. Dutch South East Cooperative Urological Group. *Urology*, 1995. 45: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/7716838>
152. Lammers, R.J., *et al.* Smoking status is a risk factor for recurrence after transurethral resection of non-muscle-invasive bladder cancer. *Eur Urol*, 2011. 60: 713.
<https://www.ncbi.nlm.nih.gov/pubmed/21794974>
153. Rink, M., *et al.* Smoking reduces the efficacy of intravesical bacillus Calmette-Guerin immunotherapy in non-muscle-invasive bladder cancer. *Eur Urol*, 2012. 62: 1204.
<https://www.ncbi.nlm.nih.gov/pubmed/22980442>
154. Rink, M., *et al.* Impact of smoking on outcomes of patients with a history of recurrent nonmuscle invasive bladder cancer. *J Urol*, 2012. 188: 2120.
<https://www.ncbi.nlm.nih.gov/pubmed/23083868>
155. Crivelli, J.J., *et al.* Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. *Eur Urol*, 2014. 65: 742.
<https://www.ncbi.nlm.nih.gov/pubmed/23810104>
156. Grotenhuis, A.J., *et al.* The effect of smoking and timing of smoking cessation on clinical outcome in non-muscle-invasive bladder cancer. *Urol Oncol*, 2015. 33: 65 e9.
<https://www.ncbi.nlm.nih.gov/pubmed/25023787>
157. Muller, J., *et al.* Trends in the risk of second primary cancer among bladder cancer survivors: a population-based cohort of 10 047 patients. *BJU Int*, 2016. 118: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/26469096>
158. Soloway, M.S., *et al.* Urothelial susceptibility to tumor cell implantation: influence of cauterization. *Cancer*, 1980. 46: 1158.
<https://www.ncbi.nlm.nih.gov/pubmed/7214299>
159. Pan, J.S., *et al.* Inhibition of implantation of murine bladder tumor by thiotepa in cauterized bladder. *J Urol*, 1989. 142: 1589.
<https://www.ncbi.nlm.nih.gov/pubmed/2511340>
160. Brocks, C.P., *et al.* Inhibition of tumor implantation by intravesical gemcitabine in a murine model of superficial bladder cancer. *J Urol*, 2005. 174: 1115.
<https://www.ncbi.nlm.nih.gov/pubmed/16094076>

161. Oosterlinck, W., *et al.* A prospective European Organization for Research and Treatment of Cancer Genitourinary Group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. *J Urol*, 1993. 149: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/8455236>
162. Sylvester, R.J., *et al.* Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation? *Eur Urol*, 2016. 69: 231.
<https://www.ncbi.nlm.nih.gov/pubmed/26091833>
163. Sylvester, R.J., *et al.* A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol*, 2004. 171: 2186.
<https://www.ncbi.nlm.nih.gov/pubmed/15126782>
164. Abern, M.R., *et al.* Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. *J Natl Compr Canc Netw*, 2013. 11: 477.
<https://www.ncbi.nlm.nih.gov/pubmed/23584348>
165. Perlis, N., *et al.* Immediate post-transurethral resection of bladder tumor intravesical chemotherapy prevents non-muscle-invasive bladder cancer recurrences: an updated meta-analysis on 2548 patients and quality-of-evidence review. *Eur Urol*, 2013. 64: 421.
<https://www.ncbi.nlm.nih.gov/pubmed/23830475>
166. Pode, D., *et al.* The mechanism of human bladder tumor implantation in an in vitro model. *J Urol*, 1986. 136: 482.
<https://www.ncbi.nlm.nih.gov/pubmed/3525861>
167. Bohle, A., *et al.* Inhibition of bladder carcinoma cell adhesion by oligopeptide combinations in vitro and in vivo. *J Urol*, 2002. 167: 357.
<https://www.ncbi.nlm.nih.gov/pubmed/11743356>
168. Oddens, J.R., *et al.* One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe? *Eur Urol*, 2004. 46: 336.
<https://www.ncbi.nlm.nih.gov/pubmed/15306104>
169. Elmamoun, M.H., *et al.* Destruction of the bladder by single dose Mitomycin C for low-stage transitional cell carcinoma (TCC)--avoidance, recognition, management and consent. *BJU Int*, 2014. 113: E34.
<https://www.ncbi.nlm.nih.gov/pubmed/24053461>
170. Bouffieux, C., *et al.* Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. *European Organization for Research and Treatment of Cancer Genitourinary Group. J Urol*, 1995. 153: 934.
<https://www.ncbi.nlm.nih.gov/pubmed/7853578>
171. Kaasinen, E., *et al.* Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. *Eur Urol*, 2002. 42: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/12160589>
172. Sylvester, R.J., *et al.* The schedule and duration of intravesical chemotherapy in patients with non-muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. *Eur Urol*, 2008. 53: 709.
<https://www.ncbi.nlm.nih.gov/pubmed/18207317>
173. Tolley, D.A., *et al.* The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. *J Urol*, 1996. 155: 1233.
<https://www.ncbi.nlm.nih.gov/pubmed/8632538>
174. Huncharek, M., *et al.* Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. *Anticancer Res*, 2001. 21: 765.
<https://www.ncbi.nlm.nih.gov/pubmed/11299841>
175. Bohle, A., *et al.* Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology*, 2004. 63: 682.
<https://www.ncbi.nlm.nih.gov/pubmed/15072879>
176. Sylvester, R.J., *et al.* Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol*, 2002. 168: 1964.
<https://www.ncbi.nlm.nih.gov/pubmed/12394686>

177. Malmstrom, P.U., *et al.* An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. *Eur Urol*, 2009. 56: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/19409692>
178. Sylvester, R.J., *et al.* Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guerin, and bacillus Calmette-Guerin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. *Eur Urol*, 2010. 57: 766.
<https://www.ncbi.nlm.nih.gov/pubmed/20034729>
179. Shang, P.F., *et al.* Intravesical Bacillus Calmette-Guerin versus epirubicin for Ta and T1 bladder cancer. *Cochrane Database Syst Rev*, 2011: CD006885.
<https://www.ncbi.nlm.nih.gov/pubmed/21563157>
180. Au, J.L., *et al.* Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. *J Natl Cancer Inst*, 2001. 93: 597.
<https://www.ncbi.nlm.nih.gov/pubmed/11309436>
181. Giesbers, A.A., *et al.* Recurrence of superficial bladder carcinoma after intravesical instillation of mitomycin-C. Comparison of exposure times. *Br J Urol*, 1989. 63: 176.
<https://www.ncbi.nlm.nih.gov/pubmed/2495144>
182. Kuroda, M., *et al.* Effect of prophylactic treatment with intravesical epirubicin on recurrence of superficial bladder cancer--The 6th Trial of the Japanese Urological Cancer Research Group (JUICRG): a randomized trial of intravesical epirubicin at dose of 20mg/40ml, 30mg/40ml, 40mg/40ml. *Eur Urol*, 2004. 45: 600.
<https://www.ncbi.nlm.nih.gov/pubmed/15082202>
183. Arends, T.J., *et al.* Combined chemohyperthermia: 10-year single center experience in 160 patients with nonmuscle invasive bladder cancer. *J Urol*, 2014. 192: 708.
<https://www.ncbi.nlm.nih.gov/pubmed/24704017>
184. Arends, T.J., *et al.* Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guerin for Adjuvant Treatment of Patients with Intermediate- and High-risk Non-Muscle-invasive Bladder Cancer. *Eur Urol*, 2016. 69: 1046.
<https://www.ncbi.nlm.nih.gov/pubmed/26803476>
185. Di Stasi, S.M., *et al.* Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol*, 2006. 7: 43.
<https://www.ncbi.nlm.nih.gov/pubmed/16389183>
186. Shelley, M.D., *et al.* A systematic review of intravesical bacillus Calmette-Guerin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. *BJU Int*, 2001. 88: 209.
<https://www.ncbi.nlm.nih.gov/pubmed/11488731>
187. Han, R.F., *et al.* Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. *Urology*, 2006. 67: 1216.
<https://www.ncbi.nlm.nih.gov/pubmed/16765182>
188. Shelley, M.D., *et al.* Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. *BJU Int*, 2004. 93: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/15008714>
189. Bohle, A., *et al.* Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol*, 2003. 169: 90.
<https://www.ncbi.nlm.nih.gov/pubmed/12478111>
190. Duchek, M., *et al.* Bacillus Calmette-Guerin is superior to a combination of epirubicin and interferon-alpha2b in the intravesical treatment of patients with stage T1 urinary bladder cancer. A prospective, randomized, Nordic study. *Eur Urol*, 2010. 57: 25.
<https://www.ncbi.nlm.nih.gov/pubmed/19819617>
191. Jarvinen, R., *et al.* Long-term efficacy of maintenance bacillus Calmette-Guerin versus maintenance mitomycin C instillation therapy in frequently recurrent TaT1 tumours without carcinoma *in situ*: a subgroup analysis of the prospective, randomised FinnBladder I study with a 20-year follow-up. *Eur Urol*, 2009. 56: 260.
<https://www.ncbi.nlm.nih.gov/pubmed/19395154>

192. Huncharek, M., *et al.* The influence of intravesical therapy on progression of superficial transitional cell carcinoma of the bladder: a metaanalytic comparison of chemotherapy versus bacilli Calmette-Guerin immunotherapy. *Am J Clin Oncol*, 2004. 27: 522.
<https://www.ncbi.nlm.nih.gov/pubmed/15596924>
193. Oddens, J.R., *et al.* The effect of age on the efficacy of maintenance bacillus calmette-guerin relative to maintenance epirubicin in patients with stage ta t1 urothelial bladder cancer: results from EORTC genito-urinary group study 30911. *Eur Urol*, 2014. 66: 694.
<https://www.ncbi.nlm.nih.gov/pubmed/24948466>
194. Rentsch, C.A., *et al.* Bacillus calmette-guerin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. *Eur Urol*, 2014. 66: 677.
<https://www.ncbi.nlm.nih.gov/pubmed/24674149>
195. Sengiku, A., *et al.* A prospective comparative study of intravesical bacillus Calmette-Guerin therapy with the Tokyo or Connaught strain for nonmuscle invasive bladder cancer. *J Urol*, 2013. 190: 50.
<https://www.ncbi.nlm.nih.gov/pubmed/23376145>
196. van der Meijden, A.P., *et al.* Maintenance Bacillus Calmette-Guerin for Ta T1 bladder tumors is not associated with increased toxicity: results from a European Organisation for Research and Treatment of Cancer Genito-Urinary Group Phase III Trial. *Eur Urol*, 2003. 44: 429.
<https://www.ncbi.nlm.nih.gov/pubmed/14499676>
197. Brausi, M., *et al.* Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. *Eur Urol*, 2014. 65: 69.
<https://www.ncbi.nlm.nih.gov/pubmed/23910233>
198. Oddens, J.R., *et al.* Increasing age is not associated with toxicity leading to discontinuation of treatment in patients with urothelial non-muscle-invasive bladder cancer randomised to receive 3 years of maintenance bacille Calmette-Guerin: results from European Organisation for Research and Treatment of Cancer Genito-Urinary Group study 30911. *BJU Int*, 2016. 118: 423.
<https://www.ncbi.nlm.nih.gov/pubmed/26945890>
199. Herr, H.W. Intravesical bacillus Calmette-Guerin outcomes in patients with bladder cancer and asymptomatic bacteriuria. *J Urol*, 2012. 187: 435.
<https://www.ncbi.nlm.nih.gov/pubmed/22177154>
200. Herr, H.W. Outpatient urological procedures in antibiotic-naive patients with bladder cancer with asymptomatic bacteriuria. *BJU Int*, 2012. 110: E658.
<https://www.ncbi.nlm.nih.gov/pubmed/22883017>
201. Lamm, D.L., *et al.* Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. *J Urol*, 1992. 147: 596.
<https://www.ncbi.nlm.nih.gov/pubmed/1538436>
202. Palou, J., *et al.* Intravesical bacillus Calmette-Guerin for the treatment of superficial bladder cancer in renal transplant patients. *Transplantation*, 2003. 76: 1514.
<https://www.ncbi.nlm.nih.gov/pubmed/14657696>
203. Yossepowitch, O., *et al.* Safety and efficacy of intravesical bacillus Calmette-Guerin instillations in steroid treated and immunocompromised patients. *J Urol*, 2006. 176: 482.
<https://www.ncbi.nlm.nih.gov/pubmed/16813873>
204. Roumeguere, T., *et al.* Bacillus Calmette-Guerin therapy in non-muscle-invasive bladder carcinoma after renal transplantation for end-stage aristolochic acid nephropathy. *Transpl Int*, 2015. 28: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/25377421>
205. Rodriguez, F., *et al.* [Practical guideline for the management of adverse events associated with BCG installations]. *Arch Esp Urol*, 2008. 61: 591.
<https://www.ncbi.nlm.nih.gov/pubmed/18709813>
206. Witjes JA, P.J., Soloway M, *et al.* Clinical practice recommendations for the prevention and management of intravesical therapy-associated adverse events. *Eur Urol Suppl*, 2008. 7: 667.
[http://www.europeanurology.com/article/S1569-9056\(08\)00110-3/abstract](http://www.europeanurology.com/article/S1569-9056(08)00110-3/abstract)
207. Palou, J., *et al.* Intravesical treatment of severe bacillus Calmette-Guerin cystitis. *Int Urol Nephrol*, 2001. 33: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/12230277>
208. Falkensammer, C., *et al.* Late occurrence of bilateral tuberculous-like epididymo-orchitis after intravesical bacille Calmette-Guerin therapy for superficial bladder carcinoma. *Urology*, 2005. 65: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/15667898>

209. Tinazzi, E., *et al.* Reactive arthritis following BCG immunotherapy for urinary bladder carcinoma: a systematic review. *Rheumatol Int*, 2006. 26: 481.
<https://www.ncbi.nlm.nih.gov/pubmed/16220289>
210. Morales, A., *et al.* Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol*, 1976. 116: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/820877>
211. Lamm, D.L., *et al.* Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma *in situ* transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol*, 2000. 163: 1124.
<https://www.ncbi.nlm.nih.gov/pubmed/10737480>
212. Zlotta, A.R., *et al.* What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? *Eur Urol*, 2000. 37: 470.
<https://www.ncbi.nlm.nih.gov/pubmed/10765079>
213. Oddens, J., *et al.* Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol*, 2013. 63: 462.
<https://www.ncbi.nlm.nih.gov/pubmed/23141049>
214. Martinez-Pineiro, L., *et al.* Maintenance Therapy with 3-monthly Bacillus Calmette-Guerin for 3 Years is Not Superior to Standard Induction Therapy in High-risk Non-muscle-invasive Urothelial Bladder Carcinoma: Final Results of Randomised CUETO Study 98013. *Eur Urol*, 2015. 68: 256.
<https://www.ncbi.nlm.nih.gov/pubmed/25794457>
215. Martinez-Pineiro, J.A., *et al.* Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guerin with a reduced dose of 27 mg in superficial bladder cancer. *BJU Int*, 2002. 89: 671.
<https://www.ncbi.nlm.nih.gov/pubmed/11966623>
216. Martinez-Pineiro, J.A., *et al.* Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. *J Urol*, 2005. 174: 1242.
<https://www.ncbi.nlm.nih.gov/pubmed/16145378>
217. Ojea, A., *et al.* A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. *Eur Urol*, 2007. 52: 1398.
<https://www.ncbi.nlm.nih.gov/pubmed/17485161>
218. Solsona, E., *et al.* Sequential combination of mitomycin C plus bacillus Calmette-Guerin (BCG) is more effective but more toxic than BCG alone in patients with non-muscle-invasive bladder cancer in intermediate- and high-risk patients: final outcome of CUETO 93009, a randomized prospective trial. *Eur Urol*, 2015. 67: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/25301758>
219. Jarvinen, R., *et al.* Long-term Outcome of Patients with Frequently Recurrent Non-muscle-invasive Bladder Carcinoma Treated with One Perioperative Plus Four Weekly Instillations of Mitomycin C Followed by Monthly Bacillus Calmette-Guerin (BCG) or Alternating BCG and Interferon-alpha2b Instillations: Prospective Randomised FinnBladder-4 Study. *Eur Urol*, 2015. 68: 611.
<https://www.ncbi.nlm.nih.gov/pubmed/25748117>
220. Marttila, T., *et al.* Intravesical Bacillus Calmette-Guerin Versus Combination of Epirubicin and Interferon-alpha2a in Reducing Recurrence of Non-Muscle-invasive Bladder Carcinoma: FinnBladder-6 Study. *Eur Urol*, 2016. 70: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/27085624>
221. Cui, J., *et al.* Combination of Intravesical Chemotherapy and Bacillus Calmette-Guerin Versus Bacillus Calmette-Guerin Monotherapy in Intermediate- and High-risk Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-analysis. *Medicine (Baltimore)*, 2016. 95: e2572.
<https://www.ncbi.nlm.nih.gov/pubmed/26817914>
222. Jakse, G., *et al.* Intravesical BCG in patients with carcinoma *in situ* of the urinary bladder: long-term results of EORTC GU Group phase II protocol 30861. *Eur Urol*, 2001. 40: 144.
<https://www.ncbi.nlm.nih.gov/pubmed/11528191>
223. Gofrit, O.N., *et al.* The natural history of bladder carcinoma *in situ* after initial response to bacillus Calmette-Guerin immunotherapy. *Urol Oncol*, 2009. 27: 258.
<https://www.ncbi.nlm.nih.gov/pubmed/18440839>

224. Sylvester, R.J., *et al.* Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma *in situ* of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol*, 2005. 174: 86.
<https://www.ncbi.nlm.nih.gov/pubmed/15947584>
225. Kaasinen, E., *et al.* Alternating mitomycin C and BCG instillations versus BCG alone in treatment of carcinoma *in situ* of the urinary bladder: a nordic study. *Eur Urol*, 2003. 43: 637.
<https://www.ncbi.nlm.nih.gov/pubmed/12767365>
226. Solsona, E., *et al.* Extravesical involvement in patients with bladder carcinoma *in situ*: biological and therapy implications. *J Urol*, 1996. 155: 895.
<https://www.ncbi.nlm.nih.gov/pubmed/8583601>
227. Palou, J., *et al.* Urothelial carcinoma of the prostate. *Urology*, 2007. 69: 50.
<https://www.ncbi.nlm.nih.gov/pubmed/17280908>
228. Palou Redorta, J., *et al.* Intravesical instillations with bacillus calmette-guerin for the treatment of carcinoma *in situ* involving prostatic ducts. *Eur Urol*, 2006. 49: 834.
<https://www.ncbi.nlm.nih.gov/pubmed/16426729>
229. Herr, H.W., *et al.* Defining bacillus Calmette-Guerin refractory superficial bladder tumors. *J Urol*, 2003. 169: 1706.
<https://www.ncbi.nlm.nih.gov/pubmed/12686813>
230. Lerner, S.P., *et al.* Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non-muscle invasive bladder cancer. *Urol Oncol*, 2009. 27: 155.
<https://www.ncbi.nlm.nih.gov/pubmed/18367117>
231. van den Bosch, S., *et al.* Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. *Eur Urol*, 2011. 60: 493.
<https://www.ncbi.nlm.nih.gov/pubmed/21664041>
232. Gallagher, B.L., *et al.* Impact of previous bacille Calmette-Guerin failure pattern on subsequent response to bacille Calmette-Guerin plus interferon intravesical therapy. *Urology*, 2008. 71: 297.
<https://www.ncbi.nlm.nih.gov/pubmed/18308107>
233. Rosevear, H.M., *et al.* Factors affecting response to bacillus Calmette-Guerin plus interferon for urothelial carcinoma *in situ*. *J Urol*, 2011. 186: 817.
<https://www.ncbi.nlm.nih.gov/pubmed/21788050>
234. Morales, A., *et al.* Efficacy and safety of MCNA in patients with nonmuscle invasive bladder cancer at high risk for recurrence and progression after failed treatment with bacillus Calmette-Guerin. *J Urol*, 2015. 193: 1135.
<https://www.ncbi.nlm.nih.gov/pubmed/25286009>
235. Cockerill, P.A., *et al.* Intravesical gemcitabine in combination with mitomycin C as salvage treatment in recurrent non-muscle-invasive bladder cancer. *BJU Int*, 2016. 117: 456.
<https://www.ncbi.nlm.nih.gov/pubmed/25682834>
236. Dalbagni, G., *et al.* Phase II trial of intravesical gemcitabine in bacille Calmette-Guerin-refractory transitional cell carcinoma of the bladder. *J Clin Oncol*, 2006. 24: 2729.
<https://www.ncbi.nlm.nih.gov/pubmed/16782913>
237. Barlow, L., *et al.* A single-institution experience with induction and maintenance intravesical docetaxel in the management of non-muscle-invasive bladder cancer refractory to bacille Calmette-Guerin therapy. *BJU Int*, 2009. 104: 1098.
<https://www.ncbi.nlm.nih.gov/pubmed/19389012>
238. Steinberg, G., *et al.* Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma *in situ* of the bladder. The Valrubicin Study Group. *J Urol*, 2000. 163: 761.
<https://www.ncbi.nlm.nih.gov/pubmed/10687972>
239. Nativ, O., *et al.* Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guerin. *J Urol*, 2009. 182: 1313.
<https://www.ncbi.nlm.nih.gov/pubmed/19683278>
240. Joudi, F.N., *et al.* Final results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. *Urol Oncol*, 2006. 24: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/16818189>
241. Di Lorenzo, G., *et al.* Gemcitabine versus bacille Calmette-Guerin after initial bacille Calmette-Guerin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. *Cancer*, 2010. 116: 1893.
<https://www.ncbi.nlm.nih.gov/pubmed/20162706>

242. Jones, G., *et al.* Intravesical gemcitabine for non-muscle invasive bladder cancer. *Cochrane Database Syst Rev*, 2012. 1: CD009294.
<https://www.ncbi.nlm.nih.gov/pubmed/22259002>
243. Turker, P., *et al.* Upstaging of urothelial cancer at the time of radical cystectomy: factors associated with upstaging and its effect on outcome. *BJU Int*, 2012. 110: 804.
<https://www.ncbi.nlm.nih.gov/pubmed/22321341>
244. May, M., *et al.* Pathological upstaging detected in radical cystectomy procedures is associated with a significantly worse tumour-specific survival rate for patients with clinical T1 urothelial carcinoma of the urinary bladder. *Scand J Urol Nephrol*, 2011. 45: 251.
<https://www.ncbi.nlm.nih.gov/pubmed/21388337>
245. Svatek, R.S., *et al.* Discrepancy between clinical and pathological stage: external validation of the impact on prognosis in an international radical cystectomy cohort. *BJU Int*, 2011. 107: 898.
<https://www.ncbi.nlm.nih.gov/pubmed/21244604>
246. Shariat, S.F., *et al.* Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. *Eur Urol*, 2007. 51: 137.
<https://www.ncbi.nlm.nih.gov/pubmed/16793197>
247. Moschini, M., *et al.* Comparing long-term outcomes of primary and progressive carcinoma invading bladder muscle after radical cystectomy. *BJU Int*, 2016. 117: 604.
<https://www.ncbi.nlm.nih.gov/pubmed/25851271>
248. Schrier, B.P., *et al.* Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. *Eur Urol*, 2004. 45: 292.
<https://www.ncbi.nlm.nih.gov/pubmed/15036673>
249. Kamat, A.M., *et al.* The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. *J Urol*, 2006. 175: 881.
<https://www.ncbi.nlm.nih.gov/pubmed/16469571>
250. Raj, G.V., *et al.* Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol*, 2007. 177: 1283.
<https://www.ncbi.nlm.nih.gov/pubmed/17382713>
251. Stein, J.P., *et al.* Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol*, 2001. 19: 666.
<https://www.ncbi.nlm.nih.gov/pubmed/11157016>
252. Hautmann, R.E., *et al.* Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. *Eur Urol*, 2012. 61: 1039.
<https://www.ncbi.nlm.nih.gov/pubmed/22381169>
253. Shariat, S.F., *et al.* Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol*, 2006. 176: 2414.
<https://www.ncbi.nlm.nih.gov/pubmed/17085118>
254. Holmang, S., *et al.* Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. *J Urol*, 2001. 165: 1124.
<https://www.ncbi.nlm.nih.gov/pubmed/11257652>
255. Gofrit, O.N., *et al.* Watchful waiting policy in recurrent Ta G1 bladder tumors. *Eur Urol*, 2006. 49: 303.
<https://www.ncbi.nlm.nih.gov/pubmed/16413659>
256. Pruthi, R.S., *et al.* Conservative management of low risk superficial bladder tumors. *J Urol*, 2008. 179: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/17997444>
257. Hernandez, V., *et al.* Long-term oncological outcomes of an active surveillance program in recurrent low grade Ta bladder cancer. *Urol Oncol*, 2016. 34: 165 e19.
<https://www.ncbi.nlm.nih.gov/pubmed/26687318>
258. Holmang, S., *et al.* Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. *J Urol*, 2002. 167: 1634.
<https://www.ncbi.nlm.nih.gov/pubmed/11912378>
259. Mariappan, P., *et al.* A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years based on a 25-year prospective database. *J Urol*, 2005. 173: 1108.
<https://www.ncbi.nlm.nih.gov/pubmed/15758711>
260. Soukup, V., *et al.* Follow-up after surgical treatment of bladder cancer: a critical analysis of the literature. *Eur Urol*, 2012. 62: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/22609313>

261. Holmang, S., *et al.* Should follow-up cystoscopy in bacillus Calmette-Guerin-treated patients continue after five tumour-free years? *Eur Urol*, 2012. 61: 503.
<https://www.ncbi.nlm.nih.gov/pubmed/22119022>
262. Niwa, N., *et al.* Comparison of outcomes between ultrasonography and cystoscopy in the surveillance of patients with initially diagnosed TaG1-2 bladder cancers: A matched-pair analysis. *Urol Oncol*, 2015. 33: 386 e15.
<https://www.ncbi.nlm.nih.gov/pubmed/26027764>

10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=panel>.

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EAU Guidelines on Urothelial Carcinoma of the Upper Urinary Tract

M. Rouprêt, M. Babjuk, M. Burger, E. Compérat,
N. Cowan, P. Gontero, A.H. Mostafid, J. Palou,
B.W.G. van Rhijn, S.F. Shariat, R. Sylvester, R. Zigeuner,
Guidelines Associates: J.L. Dominguez-Escrig,
B. Peyronnet, T. Seisen

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Non-muscle-invasive Bladder Cancer (NMIBC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of urothelial carcinoma of the upper urinary tract (UTUC). Separate EAU guidelines documents are available addressing non-muscle-invasive bladder cancer [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The European Association of Urology (EAU) Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a radiologist, a pathologist and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring urothelial carcinoma. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/upper-urinary-tracturothelial-cell-carcinoma/>.

1.3 Available publications

A quick reference document (Pocket guidelines) is available in print and in a number of versions for mobile devices, presenting the main findings of the UTUC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available as are a number of translations of all versions of the EAU UTUC Guidelines. All documents are accessible through the EAU website Uroweb: <http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/>.

1.4 Publication history & summary of changes

The first EAU guidelines on UTUC were published in 2011. The 2017 EAU guidelines on UTUC present a limited update of the 2016 version.

1.4.1 Summary of changes

The literature for the complete document has been assessed and updated, whenever relevant. Conclusions and recommendations have been rephrased and added to throughout the current document.

Key changes for the 2017 print:

New section 3.3.1.1 - Summary of evidence for Chapter 3 (Epidemiology, aetiology and pathology) has been added.

3.3.1.1 Summary of evidence for histology and classification

Summary of evidence	LE
A small proportion of upper tract urothelial carcinoma belong to the tumour spectrum of the hereditary non-polyposis colorectal cancer.	3

New section 5.3 - Summary of evidence section has been added to the Guidelines for the diagnosis of upper tract urothelial carcinoma.

5.3 Summary of evidence and guidelines for the diagnosis of upper tract urothelial carcinoma

Summary of evidence	LE
The diagnosis of urothelial carcinoma of the upper urinary depends on computed tomography urography.	2
Selective urinary cytology has high sensitivity in high-grade tumours including carcinoma <i>in situ</i> .	3

New section 7.1.2.4 – Summary of evidence section has been added to the Guidelines for radical nephroureterectomy.

7.1.2.4 Summary of evidence and guidelines for radical nephroureterectomy

Summary of evidence	LE
Radical nephroureterectomy is the standard in high-risk upper tract urothelial carcinoma, regardless of tumour location.	2
Open and laparoscopic approaches have equivalent efficacy and safety in T1–2/N0 upper tract urothelial carcinoma.	2

2. METHODS

2.1 Data identification

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. For the 2017 UTUC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive scoping exercise covering all areas of the entire guideline was performed. Excluded from the search were basic research studies, case series, reports and editorial comments. Only articles published in the English language, addressing adults were included. The search was restricted to articles published between June 1st 2015 and April 22nd 2016. Databases searched included Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 973 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?type=appendicespublications>.

References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

This document was peer-reviewed prior to publication in 2016.

2.3 Future goals

The results on ongoing and new systematic reviews will be included in the 2018 update of the UTUC Guidelines. These reviews are performed using standard Cochrane systematic review methodology: <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>.

Ongoing systematic reviews:

- Oncological outcomes of laparoscopic/robotic radical nephroureterectomy versus open radical nephroureterectomy for upper tract urothelial carcinoma: an EAU Guidelines systematic review [5].
- What are the benefits and harms of lymph node dissection (LND) during radical nephroureterectomy for upper tract urothelial carcinoma (UTUC)? [6].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

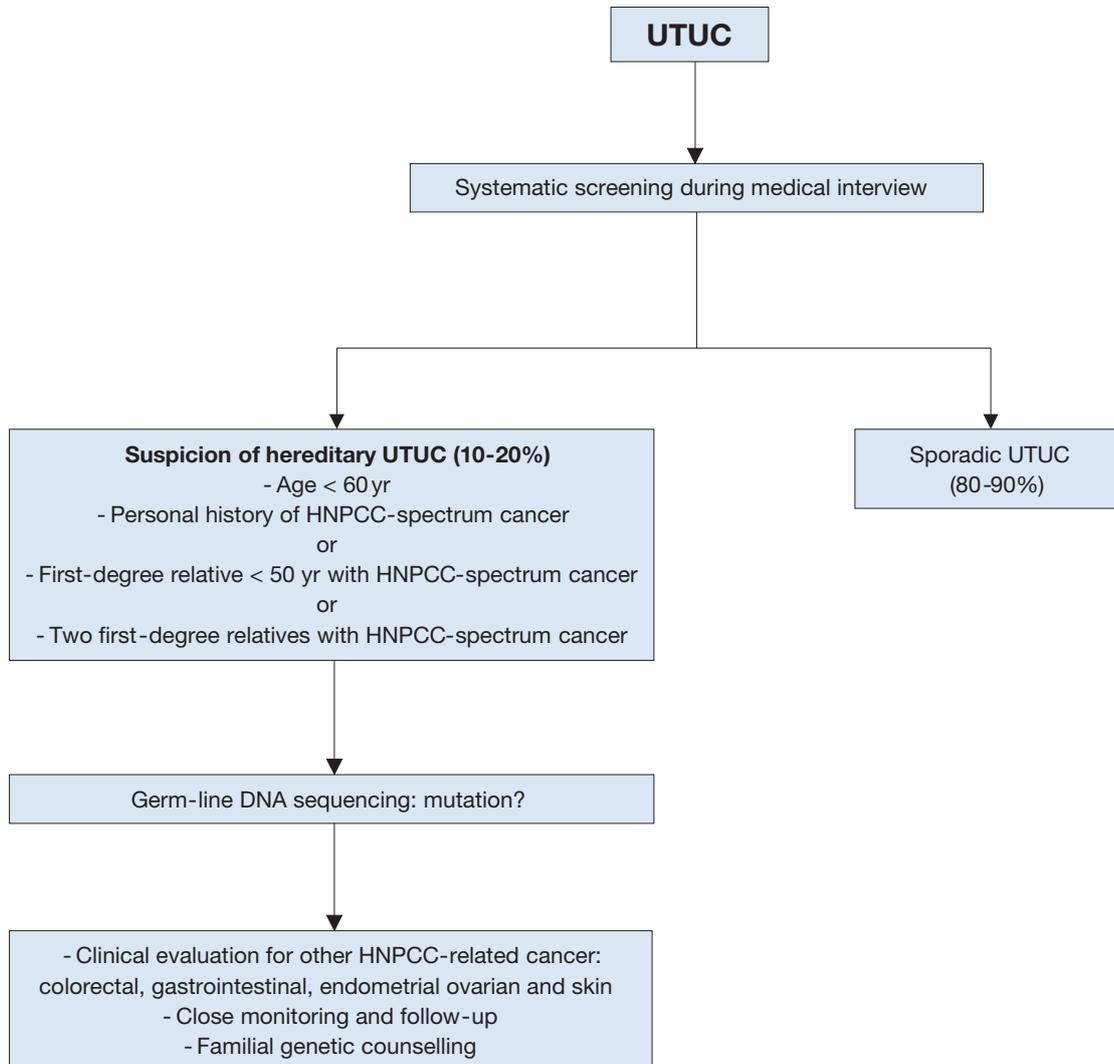
Urothelial carcinomas (UCs) are the fifth most common tumours [7]. They can be located in the lower (bladder and urethra) or upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumours account for 90-95% of UCs and are the most common malignancy of the urinary tract [8]. In contrast, UTUC are uncommon and account for only 5-10% of UCs [9, 10]. Pyelocaliceal tumours are about twice as common as ureteral tumours.

In 17% of cases, concurrent bladder cancer is present [11]. Recurrence in the bladder occurs in 22-47% of UTUC patients [12], compared with 2-6% in the contralateral upper tract [13, 14].

Approximately 60% of UTUC are invasive at diagnosis compared with 15-25% of bladder tumours [8, 15]. Upper tract urothelial carcinomas have a peak incidence in people aged 70 to 90 years and are three times more common in men [16, 17].

Familial/hereditary UTUC are linked to hereditary non-polyposis colorectal carcinoma (HNPCC) [18], which can be screened for during an interview (Figure 3.1) [19]. Patients should undergo DNA sequencing to identify hereditary cancers misclassified as sporadic if they fulfil the criteria for HNPCC [18, 20].

Figure 3.1: Selection of patients with UTUC for hereditary screening during the first medical interview



HNPCC = hereditary non-polyposis colorectal carcinoma.

3.2 Risk factors

Various environmental risk factors contribute to UTUC development [21, 22]. Tobacco exposure increases the relative risk from 2.5 to 7 [21, 23]. Historically, UTUC ‘amino tumours’ were related to occupational exposure to carcinogenic aromatic amines. The odds ratio of developing UC after exposure to aromatic amines is 8.3 [21, 22]. Upper tract urothelial carcinoma caused by phenacetin consumption almost disappeared after the product was banned in the 1970s [22].

Upper tract urothelial carcinoma often present after a bladder cancer. The average duration of exposure needed to develop UTUC is ~7 years, with a latency of ~20 years following termination of exposure.

Several studies have revealed the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis*. The aristolochic acid derivative dA-aristolactam causes a specific mutation in the p53 gene at codon 139, which occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy [22, 24, 25].

There is a high incidence of UTUC in Taiwan, especially on the South-west coast which represents 20-25% of UCs in the region [22, 25]. There is a possible association of UTUC with blackfoot disease and arsenic exposure in drinking water in this population [22, 25, 26].

Differences in the ability to counteract carcinogens may contribute to host susceptibility to UTUC. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression, which introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. Upper tract urothelial carcinoma may share some risk factors or molecular disruption pathways with bladder UC. Two UTUC-specific polymorphisms have been reported [27, 28].

3.3 Histology and classification

3.3.1 Histological types

Upper tract urothelial carcinoma with pure non-urothelial histology is an exception [29, 30] but variants are present in ~25% of cases [31, 32]. These variants always correspond to high-grade tumours with worse prognosis compared to pure UC. Squamous cell carcinoma of the upper urinary tract represents < 10% of pyelocaliceal tumours and is even rarer within the ureter. Squamous cell carcinoma of the urinary tract can be associated with chronic inflammatory and infectious diseases arising from urolithiasis [33, 34]. Other variants are: micropapillary, sarcomatoid carcinomas and lymphoepithelioma [33, 34].

3.3.1.1 Summary of evidence for histology and classification

Summary of evidence	LE
A small proportion of upper tract urothelial carcinoma belong to the tumour spectrum of the hereditary non-polyposis colorectal cancer.	3

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and bladder carcinoma are similar [8]. It is possible to distinguish between non-invasive papillary tumours (papillary urothelial tumours of low malignant potential, and low-grade and high-grade papillary UC), flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma. As in bladder tumours, non-urothelial differentiation has been identified as an adverse risk factor [35].

4.2 Tumour Node Metastasis staging

The Tumour Node Metastasis (TNM) classification is shown in Table 4.1 [36]. The regional lymph nodes that should be considered are the hilar, abdominal para-aortic, and paracaval nodes, and, for the ureter, the intrapelvic nodes. Laterality does not affect N classification.

A subclassification with pT3a and pT3b has been suggested, but is not in the officially accepted pTNM staging system [31, 37, 38]. Renal pelvic pT3 subclassification may discriminate between microscopic infiltration of the renal parenchyma (pT3a) and macroscopic infiltration or invasion of peripelvic adipose tissue. pT3b UTUC is more likely to be associated with aggressive pathologic features and disease recurrence [31, 37].

Table 4.1: TNM classification 2017 for upper tract urothelial carcinoma [36]

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i>
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.3 Histological grading

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of urothelial carcinomas which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [39, 40]. Recently an update of the 2004 WHO grading classification was published [41], but the following guidelines are still based on the 1973 and 2004 WHO classifications [39, 40].

Only few tumours of low malignant potential are found in the upper urinary tract, [33, 34]. pT2 tumours should be treated as high-grade disease.

4.4 Guidelines for staging and classification systems

Recommendations	LE	GR
Classify the depths of invasion (staging) according to Tumour Node Metastasis classification, 8 th edition.	3	A
Classify flat, high-grade tumours, confined to the mucosa, as carcinoma <i>in situ</i> (Tis).	3	A
Use the World Health Organization 1973 and 2004 grading systems for the histological classification of upper tract urothelial carcinoma.	3	A

5. DIAGNOSIS

5.1 Symptoms

The most common symptom is visible- or non-visible haematuria (70-80%) [42, 43]. Flank pain occurs in 20-40% of cases, and a lumbar mass in 10-20% [44, 45]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) are associated with UTUC and should prompt more rigorous evaluation for metastatic disease [44, 45].

5.2 Diagnosis

5.2.1 Imaging

5.2.1.1 Computed tomography urography

Computed tomography (CT) urography has the highest diagnostic accuracy for UTUC of all the clinically available imaging techniques [45]. The sensitivity of CT urography for UTUC is 0.67-1.0 and the specificity is 0.93-0.99 according to the technique used [21, 46-51]. Epithelial 'flat lesions' without mass effect or urothelial thickening are not visible with CT [52].

Computed tomography urography is defined as CT examination of the kidneys, ureters and bladder following the administration of intravenous contrast material [21, 53]. Rapid acquisition of thin sections provides high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Computed-tomography urography usually includes several phases of acquisition following administration of intravenous contrast media [21, 54].

The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [21, 53, 55, 56]. The presence of enlarged lymph nodes is highly predictive of metastasis in UTUC [21].

5.2.1.2 *Magnetic resonance imaging*

Magnetic resonance urography (MRU) is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [57]. The sensitivity of MRU is 0.75 after contrast injection for tumours < 2 cm [57]. The use of MRU with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of nephrogenic systemic fibrosis. Computed tomography urography is generally preferred over MRU for diagnosing UTUC.

5.2.2 *Cystoscopy and urinary cytology*

Positive urine cytology is suggestive of UTUC when bladder cystoscopy is normal, provided that no CIS is detected in the bladder or prostatic urethra [8, 58]. Cytology is less sensitive for UTUC than for bladder tumours. It should be performed in the upper tract (*in situ* cytology) [59].

Retrograde ureteropyelography is an option to evaluate UTUC [21, 49, 60, 61] but is now mostly used in conjunction with ureteroscopy and not as a stand-alone diagnostic technique due to similar diagnostic accuracy when compared with CT urography for UTUC [49]. Urinary cytology of the renal cavities and ureteral lumina is preferable before application of contrast agent for retrograde ureteropyelography, because the latter may cause deterioration of cytological specimens [59, 60].

The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUC parallels its performance in bladder cancer [62]. However, its use may be limited by the preponderance of low-grade recurrent disease in the population undergoing surveillance and kidney-sparing therapy for UTUC [63, 64]. FISH currently has limited value for the surveillance of UTUC [63, 64].

5.2.3 *Diagnostic ureteroscopy*

Flexible ureteroscopy is used to visualise the ureter, renal pelvis and collecting system and biopsy suspicious lesions. Ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [65]. Under-grading may occur from diagnostic biopsy, making intensive follow-up necessary if a kidney-sparing treatment is chosen [66]. Ureteroscopy also facilitates selective ureteral sampling for cytology to detect carcinoma *in situ* [60, 67, 68].

Flexible ureteroscopy is especially useful for diagnostic uncertainty, if kidney-sparing treatment is considered, or in patients with a solitary kidney. Additional information can be provided by ureteroscopy with- or without biopsy. Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology, may help in the decision-making process between radical nephroureterectomy (RNU) and endoscopic treatment [67, 69].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and the diagnosis of flat lesions [70]. Narrow-band imaging is the most promising technique to date but the results are preliminary [69, 71]. Table 5.3 lists the recommendations for diagnosis.

5.3 Summary of evidence and guidelines for the diagnosis of upper tract urothelial carcinoma

Summary of evidence	LE
The diagnosis of upper tract urothelial carcinoma depends on computed tomography urography.	2
Selective urinary cytology has high sensitivity in high-grade tumours including carcinoma <i>in situ</i> .	3

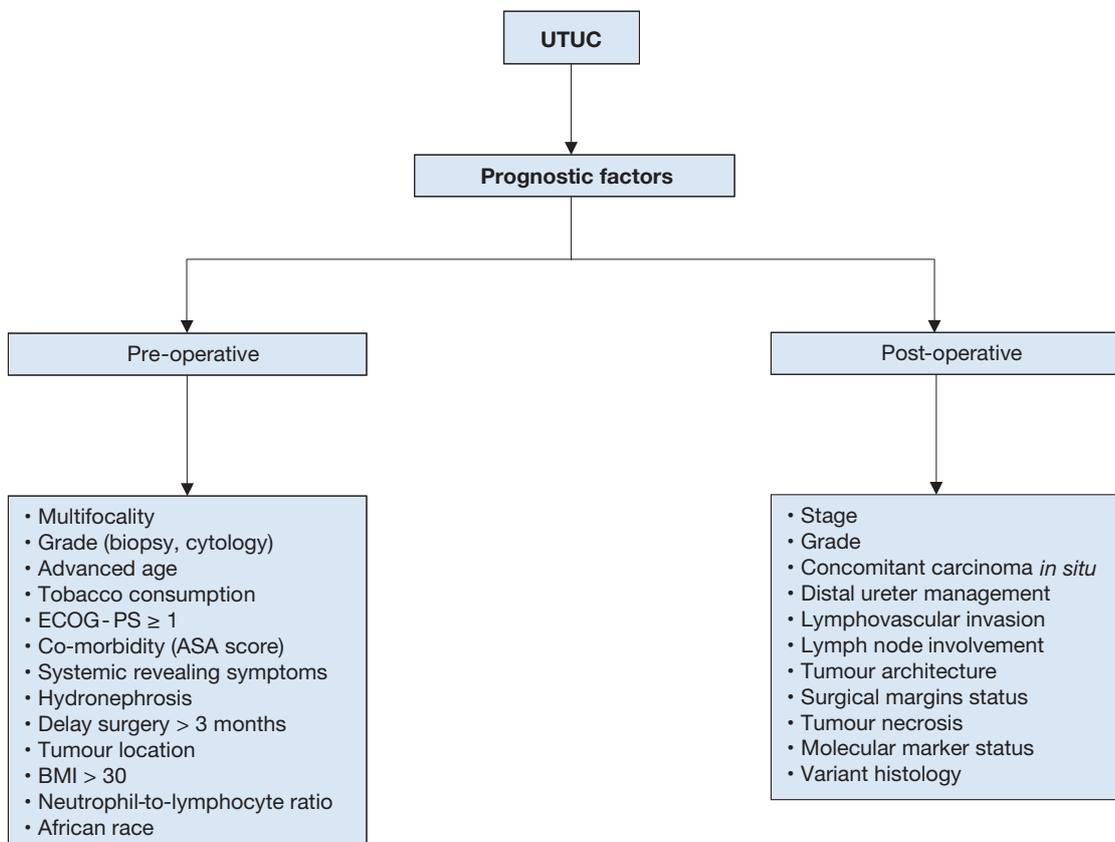
Recommendations	GR
Perform urinary cytology as part of a standard diagnostic work-up.	A
Perform a cystoscopy to rule out concomitant bladder tumour.	A
Perform a computed tomography urography for the diagnostic work-up.	A
Use diagnostic ureteroscopy and biopsy in cases where additional information will impact treatment decisions.	C

6. PROGNOSIS

6.1 Prognostic factors

Upper tract urothelial carcinomas that invade the muscle wall usually have a poor prognosis. The five-year specific survival is < 50% for patients with pT2/pT3 tumours and < 10% for those with pT4 [71-73]. The main prognostic factors are briefly listed below; Figure 6.1 presents a more exhaustive list.

Figure 6.1: Upper tract urothelial carcinoma - Prognostic factors



ASA = American Society of Anesthesiologists; BMI = body mass index;
ECOG = Eastern Cooperative Oncology Group; PS = performance score.

6.1.1 **Pre-operative factors**

6.1.1.1 *Age and sex*

Gender is no longer considered an independent prognostic factor influencing UTUC mortality [16, 73, 74]. Older age at the time of RNU is independently associated with decreased cancer-specific survival [73, 75] (LE: 3). Many elderly patients can be cured with RNU [76], suggesting that age alone is an inadequate indicator of outcome [75, 76]. Despite its association with survival, age alone should not prevent a potentially curable approach.

6.1.1.2 *Ethnicity*

One multicentre study did not show any difference between races [77] but population-based studies have indicated that African-American patients have worse outcomes compared to other ethnicities [76, 78] (LE: 3).

6.1.1.3 *Tobacco consumption*

Being a smoker at diagnosis increases the risk for disease recurrence and mortality after RNU [79, 80] as well as recurrence within the bladder [81] (LE: 3).

6.1.1.4 *Tumour location*

Initial location of the UTUC is a prognostic factor in some studies [82-84] (LE: 3). After adjustment for the effect of tumour stage, patients with ureteral and/or multifocal tumours seem to have a worse prognosis than those with renal pelvic tumours [73, 83-86].

6.1.1.5 *Surgical delay*

A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. Once a decision regarding RNU has been made the procedure should be carried-out within twelve weeks [87-90] (LE: 3).

6.1.1.6 *Other*

The American Society of Anesthesiologists (ASA) score significantly correlates with cancer-specific survival after RNU [91] (LE: 3). The Eastern Cooperative Oncology Group (ECOG) performance status correlates only with overall survival [92]. Obesity and higher body mass index adversely affect cancer-specific outcomes in UTUC [93, 94] (LE: 3). The pre-treatment derived neutrophil-lymphocyte ratio also correlates with higher cancer-specific mortality [95, 96] (LE: 3).

6.1.2 **Post-operative factors**

6.1.2.1 *Tumour stage and grade*

The primary recognised prognostic factors are tumour stage and grade [21, 67, 73, 97].

6.1.2.2 *Lymph node involvement*

Lymph node metastases and extranodal extension are powerful predictor of survival outcomes in UTUC [98]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging [99, 100] (LE: 3). Its curative role remains debated.

6.1.2.3 *Lymphovascular invasion*

Lymphovascular invasion is present in ~20% of UTUC and is an independent predictor of survival [101, 102]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [101, 103] (LE: 3).

6.1.2.4 *Surgical margins*

Positive soft tissue surgical margin after RNU is a significant factor for developing UTUC recurrence. Pathologists should look for, and report, positive margins at the level of ureteral transection, bladder cuff, and around the tumour soft tissue margin [104] (LE: 3).

6.1.2.5 *Pathological factors*

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [105, 106] (LE: 3). The architecture of UTUC is also a strong prognosticator with sessile growth pattern being associated with worse outcome [107, 108] (LE: 3). Concomitant CIS in organ-confined UTUC, and a history of bladder CIS are associated with a higher risk of disease recurrence and cancer-specific mortality [109-111] (LE: 3). Similar to lower tract UC, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease [112].

6.2 Molecular markers

Several studies have investigated the prognostic impact of markers related to cell adhesion (E-cadherin and CD24), cell differentiation (Snail and epidermal growth factor receptor), angiogenesis (hypoxia-inducible factor-1 α and metalloproteinases), cell proliferation (Ki67), epithelial-mesenchymal transition (Snail), mitosis (Aurora-A), apoptosis (Bcl-2 and survivin), vascular invasion (RON), c-met protein (MET) and mTOR pathway [21, 73, 113-117]. Microsatellite instability (MSI) is an independent molecular prognostic marker [118] and can help detect germline mutations and hereditary cancers [18].

The rarity of UTUC means that the main limitations of the above studies were their retrospective nature and small sample size. None of the markers have fulfilled the criteria necessary to support their introduction in daily clinical decision-making.

6.3 Predictive tools

Accurate predictive tools are rare for UTUC. There are two models in a pre-operative setting: one in locally advanced cancer that can guide the extent of LND at the time of RNU [119]; and one for selection of non-organ-confined UTUC likely to benefit from RNU [120]. Four nomograms are available predicting survival rates post-operatively, based on standard pathological features [121-125].

6.4 Bladder recurrence

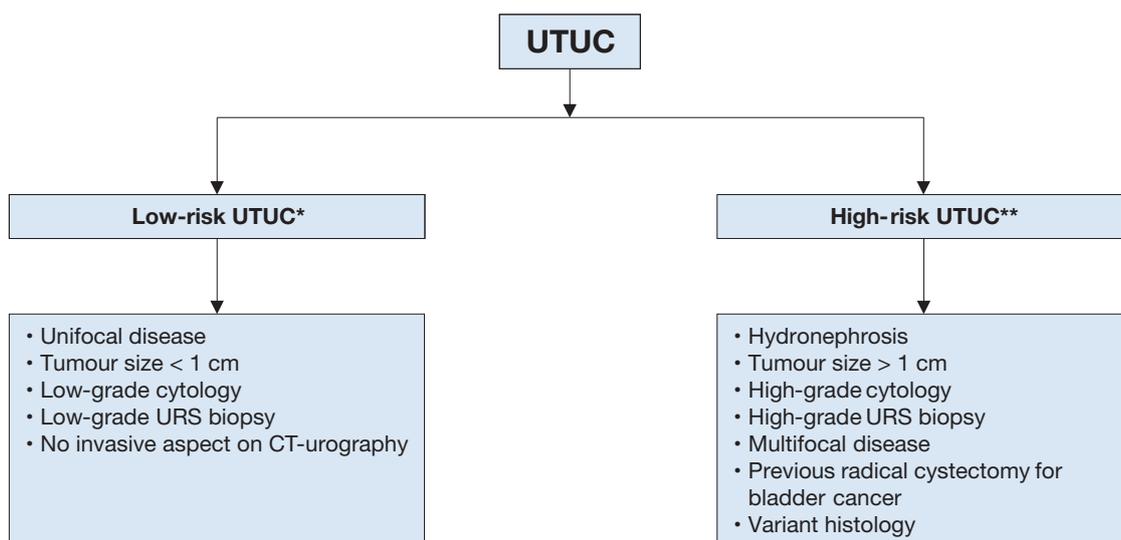
A recent meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [12] (LE: 3). Three categories of predictors of increased risk for bladder recurrence were identified:

- patient-specific factors such as (male gender, previous bladder cancer, pre-operative chronic kidney disease);
- tumour-specific factors such as (positive pre-operative urinary cytology, ureteral location, multifocality, invasive pT stage, necrosis);
- treatment-specific factors such as (laparoscopic approach, extravesical bladder cuff removal, positive surgical margins) [12].

6.5 Risk stratification

As tumour stage is difficult to assert clinically in UTUC, It is useful to 'risk stratify' UTUC between low- and high-risk tumours to identify those that are more suitable for kidney-sparing treatment rather than radical extirpative surgery [126, 127] (Figure 6.2).

Figure 6.2: Pre-intervention risk stratification of upper tract urothelial carcinoma



*All of these factors need to be present

** Any of these factors need to be present

CTU = computed tomography urography; URS = ureterorenoscopy.

6.6 Summary of evidence and guidelines for prognosis

Summary of evidence	LE
Age, sex and ethnicity are no longer considered as independent prognostic factors.	3
The primary recognised post-operative prognostic factors are tumour stage and grade, extranodal extension and lymphovascular invasion.	3

Recommendations	LE	GR
Use microsatellite instability as an independent molecular prognostic marker to help detect germline mutations and hereditary cancers.	3	C
Use the American Society of Anesthesiologists score to assess cancer-specific survival following surgery.	3	C

7. DISEASE MANAGEMENT

7.1 Localised disease

7.1.1 Kidney-sparing surgery

Kidney-sparing surgery (KSS) for low-risk UTUC (Section 7.1.1.4) allows sparing the morbidity associated with radical surgery, without compromising oncological outcomes and kidney function [128]. In low-risk cancers it is the primary approach and survival is similar after KSS versus RNU [129]. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney [21, 130, 131]. In high-risk tumours it can be considered in imperative cases (i.e. renal insufficiency or solitary functional kidney).

7.1.1.1 Ureteroscopy

Endoscopic ablation can be considered in patients with clinically low-risk cancer in the following situations [132, 133]:

- laser generator [134] and pliers are available for biopsies [133, 135] (LE: 3);
- in case a flexible ureteroscope is available (rather than a rigid ureteroscope);
- the patient is informed of the need for closer, more stringent, surveillance;
- complete tumour resection can be achieved.

Nevertheless, a risk of under-staging and under-grading remains with endoscopic management.

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-risk UTUC in the renal cavities [21, 133, 136] (LE: 3). This may be offered for low-risk tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible ureteroscopy. However, this approach is being used less due to the availability of improved materials and advances in distal-tip deflection of recent ureteroscopes [21, 133, 136].

7.1.1.3 Surgical open approach

Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading, while preserving the ipsilateral kidney. A lymphadenectomy can also be achieved during segmental ureteral resection.

Complete distal ureterectomy with neocystostomy are indicated for low-risk tumours in the distal ureter that cannot be removed completely endoscopically, and for high-risk tumours when kidney-sparing surgery for renal function preservation is necessary [21, 137, 138] (LE: 3).

Segmental resection of the iliac and lumbar ureter is associated with higher failure rates than for the distal pelvic ureter [21, 137, 138] (LE: 3).

Partial pyelectomy or partial nephrectomy is almost never indicated. Open resection of tumours of the renal pelvis or calices has almost disappeared.

7.1.1.4 Guidelines for kidney-sparing management of upper tract urothelial carcinoma

Recommendations	GR
Offer kidney-sparing management as primary treatment option to patients with low-risk tumour and two functional kidneys.	C
Offer kidney-sparing management in patients with solitary kidney and/or impaired renal function, providing it will not compromise the oncological outcome. This decision will have to be made on a case-by-case basis, engaging the patient in a shared decision-making process.	C
Offer a kidney-sparing approach in high-risk cancers for distal ureteral tumours and in imperative cases (solitary kidney and/or impaired renal function).	C
Use a laser for endoscopic treatment of upper tract urothelial carcinoma.	C

7.1.1.5 Adjuvant topical agents

The antegrade instillation of bacillus Calmette-Guérin (BCG) vaccine or mitomycin C in the upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete tumour eradication) is feasible after kidney-sparing management or for treatment of CIS [139] (LE: 3). Retrograde instillation through a ureteric catheter is also used. The reflux obtained from a double-J stent has been used, but is not advisable since it often does not reach the renal pelvis [140].

7.1.2 Radical nephroureterectomy

Open RNU with bladder cuff excision is the standard treatment for high-risk UTUC, regardless of tumour location [15] (LE: 3). Radical nephroureterectomy must comply with oncological principles, that is preventing tumour seeding by avoidance of entry into the urinary tract during resection [15].

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area. After removal of the proximal ureter, it is difficult to image or approach it by endoscopy [21, 137, 141].

Several techniques have been considered to simplify distal ureter resection, including pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception [13, 21, 141]. Except for ureteral stripping, none of these techniques is inferior to bladder cuff excision [75-77, 83] (LE: 3).

7.1.2.1 Laparoscopic radical nephroureterectomy

Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in few cases [142, 143].

Several precautions may lower the risk of tumour spillage:

- avoid entering the urinary tract;
- avoid direct contact between instruments and the tumour;
- laparoscopic RNU must take place in a closed system. Avoid morcellation of the tumour and use an endobag for tumour extraction;
- the kidney and ureter must be removed *en-bloc* with the bladder cuff;
- invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU until proven otherwise.

Laparoscopic RNU is safe in experienced hands when adhering to strict oncologic principles. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU [21, 143-147] (LE: 3).

Only one prospective randomised study has shown that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC. In contrast, oncological outcomes were in favour of the open approach in pT3 and/or high-grade tumours [148] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and refinements in staging and surgical technique [149] (LE: 3). A robot-assisted laparoscopic approach can be considered, but solid data are still lacking [150].

7.1.2.2 Lymph node dissection

The anatomic sites of lymph node drainage have not been clearly defined yet. The use of a LND template is likely to have a greater impact on patient survival than the number of removed lymph nodes [134].

Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2-4 tumours [98]. An increase in the probability of lymph-node-positive disease is related to pT classification [100]. However, it is likely that the true rate of node-positive disease has been under-reported because these data are retrospective.

Despite available studies evaluating templates to date, it is not possible to standardise indication

or extent of LND [151, 152]. Lymph node dissection can be achieved following lymphatic drainage as follows: LND on the side of the affected ureter, retroperitoneal LND for higher ureteral tumour and/or tumour of the renal pelvis (i.e. right side: border vena cava or right side of the aorta; and left side: border aorta) [21, 98].

7.1.2.3 Adjuvant bladder instillation

The rate of bladder recurrence after RNU for UTUC is 22-47% [12, 153]. Two prospective randomised trials have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) immediately after surgery reduces the risk of bladder tumour recurrence within the first year post-RNU [154-156] (LE: 1b).

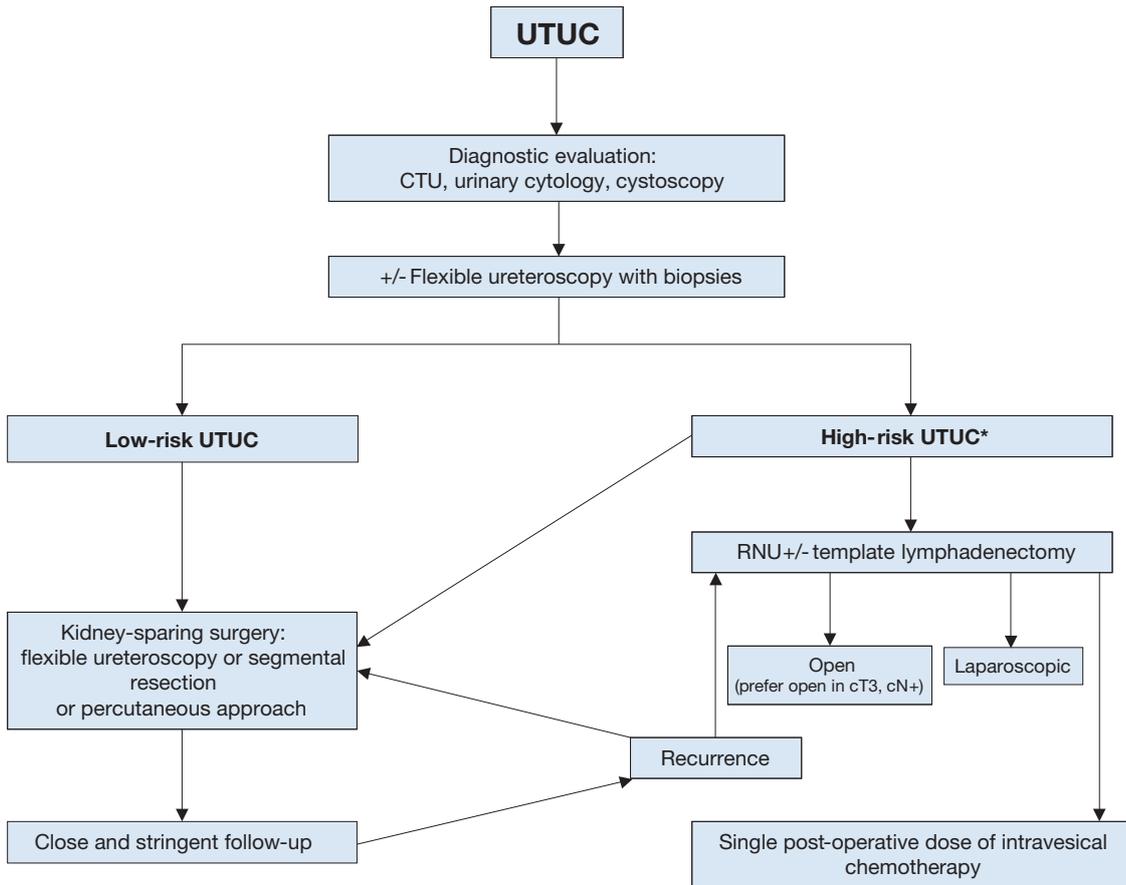
7.1.2.4 Summary of evidence and guidelines for radical nephroureterectomy

Summary of evidence	LE
Radical nephroureterectomy is the standard in high-risk upper tract urothelial carcinoma, regardless of tumour location.	2
Open and laparoscopic approaches have equivalent efficacy and safety in T1-2/N0 upper tract urothelial carcinoma.	2

Recommendations	GR
Perform radical nephroureterectomy in the following situations: <ul style="list-style-type: none"> suspicion of infiltrating upper tract urothelial carcinoma on imaging; high-grade tumour (urinary cytology); multifocality (with two functional kidneys); non-invasive but large (> 1 cm) upper tract urothelial carcinoma. 	B
Technical steps of radical nephroureterectomy:	
Remove the bladder cuff.	A
Perform a lymphadenectomy in invasive upper tract urothelial carcinoma.	C
Offer a post-operative bladder instillation to lower the bladder recurrence rate.	B

Management is outlined in Figures 7.1 and Figure 7.2.

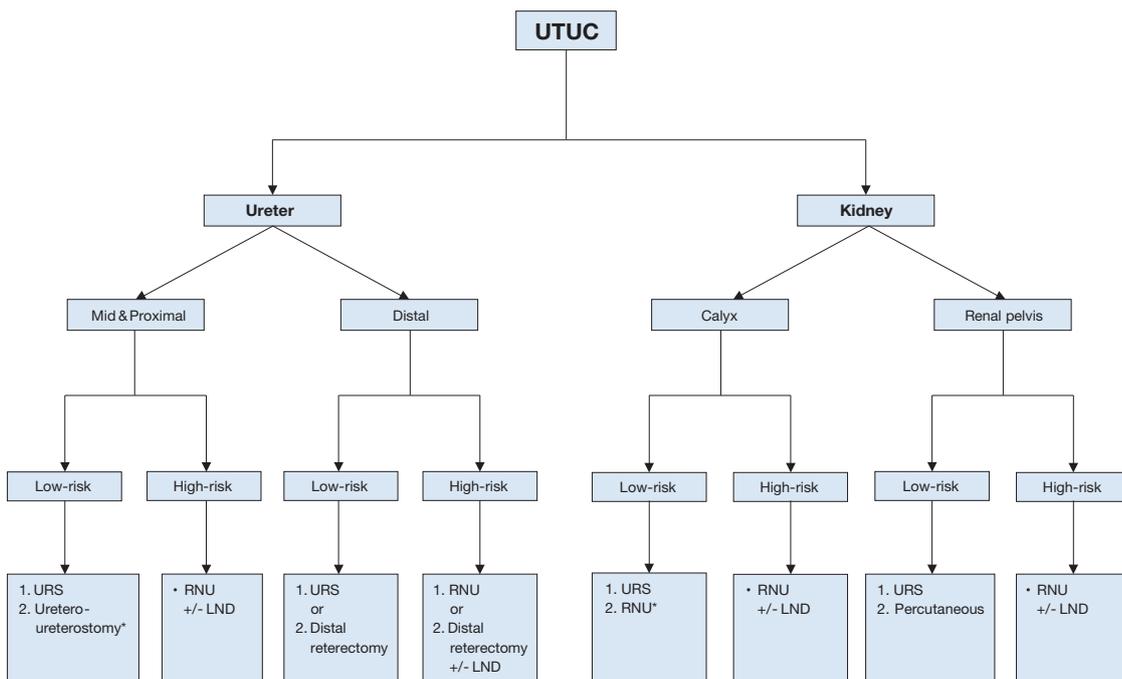
Figure 7.1: Proposed flowchart for the management of localised upper tract urothelial carcinoma



CTU = computed tomography urography; RNU = radical nephroureterectomy.

*In patients with a solitary kidney, consider a more conservative approach.

Figure 7.2: Surgical treatment according to location and risk status



1. First treatment option

2. Secondary treatment option

*In case not amendable to endoscopic management.

7.2 Advanced disease

7.2.1 Radical nephroureterectomy

There is no oncologic benefit for RNU in patients with metastatic UTUC except for palliative considerations [15, 100] (LE: 3).

7.2.2 Systemic chemotherapy

Extrapolating from the bladder cancer literature and small, single centre UTUC studies, platinum-based combination chemotherapy is expected to be efficacious in UTUC. However, there are currently insufficient data upon which to base recommendations.

There are several platinum-based regimens [157], but not all patients can receive adjuvant chemotherapy because of comorbidities and impaired renal function after radical surgery. Chemotherapy-related toxicity, particularly nephrotoxicity from platinum derivatives, may significantly affect survival in patients with post-operative renal dysfunction [158, 159].

There were no adverse effects of neoadjuvant chemotherapy for UTUC in the only study published to date [160], although survival data need to mature and longer follow-up is awaited. Adjuvant chemotherapy can achieve a recurrence-free rate of < 50% [161, 162].

After a recent comprehensive search of studies examining the role of peri-operative chemotherapy for UTUC, there appears to be an overall survival and disease-free survival benefit for cisplatin-based adjuvant chemotherapy [163] (LE: 3). However, there are currently insufficient data to base recommendations on until further evidence from an ongoing prospective trial is available [164].

7.2.3 Radiotherapy

The role of adjuvant radiotherapy is not well defined, neither alone, nor in combination with chemotherapy [21, 165] (LE: 3). It may be of benefit in terms of loco-regional and bladder control in selected patients but data are too scarce to give recommendations.

7.2.4 Summary of evidence and guideline for advanced disease

Summary of evidence	LE
Peri-operative systemic cisplatin-based chemotherapy may provide a survival benefit.	3

Recommendation	LE	GR
In case chemotherapy is offered, a neoadjuvant approach is recommended, as the renal function will decrease after radical nephroureterectomy.	3	C

8. FOLLOW-UP

The risk of disease recurrence and death evolves in the follow-up period after surgery and is less likely with time [166, 167]. Stringent follow-up (Section 8.1) is mandatory to detect metachronous bladder tumours [13], local recurrence, and distant metastases. When RNU is performed, local recurrence is rare and the risk of distant metastases is directly related to the risk factors listed previously.

Surveillance regimens are based on cystoscopy and urinary cytology for > 5 years [11-13]. Bladder recurrence is not a distant recurrence [12]. When kidney-sparing surgery is performed, the ipsilateral UUT requires careful follow-up due to the high risk of disease recurrence [130, 135, 168]. Despite endourological improvements, follow-up after kidney-sparing surgery is difficult; frequent and repeated endoscopic procedures are mandatory. As done in bladder cancer, a second look has been proposed after KSS but is not yet routine practice [169].

8.1 Summary of evidence and guidelines for follow-up of upper tract urothelial carcinoma patients after initial treatment

Summary of evidence	LE
Follow-up is more frequent and more strict in patients who have undergone kidney-sparing treatment compared to radical nephroureterectomy.	3

Recommendations	GR
After radical nephroureterectomy, > five years	
<i>Non-invasive tumour</i>	
Perform cystoscopy/urinary cytology at three months, and then annually.	C
Perform computed tomography urography every year.	C
<i>Invasive tumour</i>	
Perform cystoscopy/urinary cytology at three months, and then annually.	C
Perform computed tomography urography every six months for two years, and then annually.	C
After kidney-sparing management, > five years	
Perform urinary cytology and computed tomography urography at three and six months, and then annually.	C
Perform cystoscopy, ureteroscopy and cytology <i>in situ</i> at three and six months, and then every six months for two years, and then annually.	C

9. REFERENCES

- Babjuk, M., *et al.*, EAU Guidelines on Non-muscle-invasive Bladder Cancer (T1, T1 and CIS), in *EAU Guidelines, Edn. presented at the 32nd EAU Annual Congress, London. 2017*, EAU Guidelines Office Arnhem, The Netherlands.
- Witjes, J.A., *et al.*, EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer in *EAU Guidelines, Edn. presented at the 32nd EAU Annual Congress, London. 2017*, EAU Guidelines Office Arnhem, The Netherlands.
- Gakis, G., *et al.*, EAU Guidelines on Primary Urethral Carcinoma, in *EAU Guidelines, Edn. presented at the EAU Annual Congress, London. 2017*, EAU Guidelines Office Arnhem, The Netherlands.
- Bob Phillips, C.B., Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2009).
- Peyronnet, B., *et al.* Oncological outcomes of laparoscopic/robotic nephroureterectomy versus open nephroureterectomy for upper tract urothelial carcinoma: an EAU Guidelines systematic review. *Eur Urol Focus*, 2017. Prior to print, 2017.
- Bruins, M., *et al.* What are the benefits and harms of lymph node dissection (LND) during radical nephroureterectomy for upper tract urothelial carcinoma (UTUC)? PROSPERO International prospective register of systematic reviews, 2015.
- Siegel, R.L., *et al.* Cancer statistics, 2016. *CA Cancer J Clin*, 2016. 66: 7.
- Babjuk, M., *et al.* EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. *Eur Urol*, 2016.
- Siegel, R.L., *et al.* Cancer statistics, 2015. *CA Cancer J Clin*, 2015. 65: 5.
- Munoz, J.J., *et al.* Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. *J Urol*, 2000. 164: 1523.
- Cosentino, M., *et al.* Upper urinary tract urothelial cell carcinoma: location as a predictive factor for concomitant bladder carcinoma. *World J Urol*, 2013. 31: 141.
- Seisen, T., *et al.* A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. *Eur Urol*, 2015. 67: 1122.
- Li, W.M., *et al.* Oncologic outcomes following three different approaches to the distal ureter and bladder cuff in nephroureterectomy for primary upper urinary tract urothelial carcinoma. *Eur Urol*, 2010. 57: 963.

14. Novara, G., *et al.* Independent predictors of contralateral metachronous upper urinary tract transitional cell carcinoma after nephroureterectomy: multi-institutional dataset from three European centers. *Int J Urol*, 2009. 16: 187.
15. Margulis, V., *et al.* Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer*, 2009. 115: 1224.
16. Shariat, S.F., *et al.* Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. *World J Urol*, 2011. 29: 481.
17. Lughezzani, G., *et al.* Gender-related differences in patients with stage I to III upper tract urothelial carcinoma: results from the Surveillance, Epidemiology, and End Results database. *Urology*, 2010. 75: 321.
18. Roupret, M., *et al.* Upper urinary tract urothelial cell carcinomas and other urological malignancies involved in the hereditary nonpolyposis colorectal cancer (lynch syndrome) tumor spectrum. *Eur Urol*, 2008. 54: 1226.
19. Audenet, F., *et al.* A proportion of hereditary upper urinary tract urothelial carcinomas are misclassified as sporadic according to a multi-institutional database analysis: proposal of patient-specific risk identification tool. *BJU Int*, 2012. 110: E583.
20. Acher, P., *et al.* Towards a rational strategy for the surveillance of patients with Lynch syndrome (hereditary non-polyposis colon cancer) for upper tract transitional cell carcinoma. *BJU Int*, 2010. 106: 300.
21. Roupret, M., *et al.* European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update. *Eur Urol*, 2015. 68: 868.
22. Colin, P., *et al.* Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. *BJU Int*, 2009. 104: 1436.
23. Crivelli, J.J., *et al.* Effect of smoking on outcomes of urothelial carcinoma: a systematic review of the literature. *Eur Urol*, 2014. 65: 742.
24. Grollman, A.P., *et al.* Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci U S A*, 2007. 104: 12129.
25. Chen, C.H., *et al.* Aristolochic acid-associated urothelial cancer in Taiwan. *Proc Natl Acad Sci U S A*, 2012. 109: 8241.
26. Chiou, H.Y., *et al.* Incidence of transitional cell carcinoma and arsenic in drinking water: a follow-up study of 8,102 residents in an arseniasis-endemic area in northeastern Taiwan. *Am J Epidemiol*, 2001. 153: 411.
27. Roupret, M., *et al.* Genetic variability in 8q24 confers susceptibility to urothelial carcinoma of the upper urinary tract and is linked with patterns of disease aggressiveness at diagnosis. *J Urol*, 2012. 187: 424.
28. Roupret, M., *et al.* Phenol sulfotransferase SULT1A1*2 allele and enhanced risk of upper urinary tract urothelial cell carcinoma. *Cancer Epidemiol Biomarkers Prev*, 2007. 16: 2500.
29. Sakano, S., *et al.* Impact of variant histology on disease aggressiveness and outcome after nephroureterectomy in Japanese patients with upper tract urothelial carcinoma. *Int J Clin Oncol*, 2015. 20: 362.
30. Ouzzane, A., *et al.* Small cell carcinoma of the upper urinary tract (UUT-SCC): report of a rare entity and systematic review of the literature. *Cancer Treat Rev*, 2011. 37: 366.
31. Rink, M., *et al.* Impact of histological variants on clinical outcomes of patients with upper urinary tract urothelial carcinoma. *J Urol*, 2012. 188: 398.
32. Masson-Lecomte, A., *et al.* Impact of micropapillary histological variant on survival after radical nephroureterectomy for upper tract urothelial carcinoma. *World J Urol*, 2014. 32: 531.
33. Olgac, S., *et al.* Urothelial carcinoma of the renal pelvis: a clinicopathologic study of 130 cases. *Am J Surg Pathol*, 2004. 28: 1545.
34. Perez-Montiel, D., *et al.* High-grade urothelial carcinoma of the renal pelvis: clinicopathologic study of 108 cases with emphasis on unusual morphologic variants. *Mod Pathol*, 2006. 19: 494.
35. Tang, Q., *et al.* The prognostic impact of squamous and glandular differentiation for upper tract urothelial carcinoma patients after radical nephroureterectomy. *World J Urol*, 2016. 34: 871.
36. Brierley JD., *et al.* TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. 2017, Oxford.
37. Roscigno, M., *et al.* International validation of the prognostic value of subclassification for AJCC stage pT3 upper tract urothelial carcinoma of the renal pelvis. *BJU Int*, 2012. 110: 674.
38. Park, J., *et al.* Reassessment of prognostic heterogeneity of pT3 renal pelvic urothelial carcinoma: analysis in terms of proposed pT3 subclassification systems. *J Urol*, 2014. 192: 1064.

39. Sauter G, A.F., Amin M, *et al.*, Tumours of the urinary system: non-invasive urothelial neoplasias. In: WHO classification of classification of tumours of the urinary system and male genital organs., in *Tumours of the urinary system: non-invasive urothelial neoplasias. In: WHO classification of classification of tumours of the urinary system and male genital organs.* A.F. Sauter G, Amin M, *et al.*, Editor. 2004, IARCC Press: Lyon.
40. Epstein, J.I., *et al.* The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol*, 1998. 22: 1435.
41. Moch, H., *et al.*, WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed. ed, ed. O. H. 2016, Lyon, France.
42. Inman, B.A., *et al.* Carcinoma of the upper urinary tract: predictors of survival and competing causes of mortality. *Cancer*, 2009. 115: 2853.
43. Cowan, N.C. CT urography for hematuria. *Nat Rev Urol*, 2012. 9: 218.
44. Raman, J.D., *et al.* Does preoperative symptom classification impact prognosis in patients with clinically localized upper-tract urothelial carcinoma managed by radical nephroureterectomy? *Urol Oncol*, 2011. 29: 716.
45. Ito, Y., *et al.* Preoperative hydronephrosis grade independently predicts worse pathological outcomes in patients undergoing nephroureterectomy for upper tract urothelial carcinoma. *J Urol*, 2011. 185: 1621.
46. Chow, L.C., *et al.* Split-bolus MDCT urography with synchronous nephrographic and excretory phase enhancement. *AJR Am J Roentgenol*, 2007. 189: 314.
47. Maheshwari, E., *et al.* Split-bolus MDCT urography: Upper tract opacification and performance for upper tract tumors in patients with hematuria. *AJR Am J Roentgenol*, 2010. 194: 453.
48. Sudakoff, G.S., *et al.* Multidetector computerized tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. *J Urol*, 2008. 179: 862.
49. Wang, L.J., *et al.* Diagnostic accuracy of transitional cell carcinoma on multidetector computerized tomography urography in patients with gross hematuria. *J Urol*, 2009. 181: 524.
50. Wang, L.J., *et al.* Multidetector computerized tomography urography is more accurate than excretory urography for diagnosing transitional cell carcinoma of the upper urinary tract in adults with hematuria. *J Urol*, 2010. 183: 48.
51. Jinzaki, M., *et al.* Comparison of CT urography and excretory urography in the detection and localization of urothelial carcinoma of the upper urinary tract. *AJR Am J Roentgenol*, 2011. 196: 1102.
52. Xu, A.D., *et al.* Significance of upper urinary tract urothelial thickening and filling defect seen on MDCT urography in patients with a history of urothelial neoplasms. *AJR Am J Roentgenol*, 2010. 195: 959.
53. Van Der Molen, A.J., *et al.* CT urography: definition, indications and techniques. A guideline for clinical practice. *Eur Radiol*, 2008. 18: 4.
54. Vrtiska, T.J., *et al.* Spatial resolution and radiation dose of a 64-MDCT scanner compared with published CT urography protocols. *AJR Am J Roentgenol*, 2009. 192: 941.
55. Messer, J.C., *et al.* Multi-institutional validation of the ability of preoperative hydronephrosis to predict advanced pathologic tumor stage in upper-tract urothelial carcinoma. *Urologic oncology*, 2013. 31: 904.
56. Hurel, S., *et al.* Influence of preoperative factors on the oncologic outcome for upper urinary tract urothelial carcinoma after radical nephroureterectomy. *World J Urol*, 2015. 33: 335.
57. Takahashi, N., *et al.* Gadolinium enhanced magnetic resonance urography for upper urinary tract malignancy. *J Urol*, 2010. 183: 1330.
58. Witjes, J.A., *et al.* Hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: review of the evidence and recommendations. *Eur Urol*, 2010. 57: 607.
59. Messer, J., *et al.* Urinary cytology has a poor performance for predicting invasive or high-grade upper-tract urothelial carcinoma. *BJU Int*, 2011. 108: 701.
60. Lee, K.S., *et al.* MR urography versus retrograde pyelography/ureteroscopy for the exclusion of upper urinary tract malignancy. *Clin Radiol*, 2010. 65: 185.
61. Cowan, N.C., *et al.* Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. *BJU Int*, 2007. 99: 1363.
62. Reynolds, J.P., *et al.* Comparison of urine cytology and fluorescence *in situ* hybridization in upper urothelial tract samples. *Cancer Cytopathol*, 2014. 122: 459.

63. Johannes, J.R., *et al.* Voided urine fluorescence *in situ* hybridization testing for upper tract urothelial carcinoma surveillance. *J Urol*, 2010. 184: 879.
64. Chen, A.A., *et al.* Is there a role for FISH in the management and surveillance of patients with upper tract transitional-cell carcinoma? *J Endourol*, 2008. 22: 1371.
65. Rojas, C.P., *et al.* Low biopsy volume in ureteroscopy does not affect tumor biopsy grading in upper tract urothelial carcinoma. *Urologic oncology*, 2013. 31: 1696.
66. Smith, A.K., *et al.* Inadequacy of biopsy for diagnosis of upper tract urothelial carcinoma: implications for conservative management. *Urology*, 2011. 78: 82.
67. Clements, T., *et al.* High-grade ureteroscopic biopsy is associated with advanced pathology of upper-tract urothelial carcinoma tumors at definitive surgical resection. *J Endourol*, 2012. 26: 398.
68. Ishikawa, S., *et al.* Impact of diagnostic ureteroscopy on intravesical recurrence and survival in patients with urothelial carcinoma of the upper urinary tract. *J Urol*, 2010. 184: 883.
69. Brien, J.C., *et al.* Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. *J Urol*, 2010. 184: 69.
70. Bus, M.T., *et al.* Optical diagnostics for upper urinary tract urothelial cancer: technology, thresholds, and clinical applications. *J Endourol*, 2015. 29: 113.
71. Abouassaly, R., *et al.* Troubling outcomes from population-level analysis of surgery for upper tract urothelial carcinoma. *Urology*, 2010. 76: 895.
72. Jeldres, C., *et al.* A population-based assessment of perioperative mortality after nephroureterectomy for upper-tract urothelial carcinoma. *Urology*, 2010. 75: 315.
73. Lughezzani, G., *et al.* Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. *Eur Urol*, 2012. 62: 100.
74. Fernandez, M.I., *et al.* Evidence-based sex-related outcomes after radical nephroureterectomy for upper tract urothelial carcinoma: results of large multicenter study. *Urology*, 2009. 73: 142.
75. Shariat, S.F., *et al.* Advanced patient age is associated with inferior cancer-specific survival after radical nephroureterectomy. *BJU Int*, 2010. 105: 1672.
76. Chromecki, T.F., *et al.* Chronological age is not an independent predictor of clinical outcomes after radical nephroureterectomy. *World J Urol*, 2011. 29: 473.
77. Matsumoto, K., *et al.* Racial differences in the outcome of patients with urothelial carcinoma of the upper urinary tract: an international study. *BJU Int*, 2011. 108: E304.
78. Hosain, G.M., *et al.* Racial/ethnic differences in upper-tract urothelial cancer. *Ethn Dis*, 2012. 22: 295.
79. Rink, M., *et al.* Impact of smoking on oncologic outcomes of upper tract urothelial carcinoma after radical nephroureterectomy. *Eur Urol*, 2013. 63: 1082.
80. Simsir, A., *et al.* Prognostic factors for upper urinary tract urothelial carcinomas: stage, grade, and smoking status. *Int Urol Nephrol*, 2011. 43: 1039.
81. Xylinas, E., *et al.* Impact of smoking status and cumulative exposure on intravesical recurrence of upper tract urothelial carcinoma after radical nephroureterectomy. *BJU Int*, 2014. 114: 56.
82. Isbarn, H., *et al.* Location of the primary tumor is not an independent predictor of cancer specific mortality in patients with upper urinary tract urothelial carcinoma. *J Urol*, 2009. 182: 2177.
83. Yafi, F.A., *et al.* Impact of tumour location versus multifocality in patients with upper tract urothelial carcinoma treated with nephroureterectomy and bladder cuff excision: a homogeneous series without perioperative chemotherapy. *BJU Int*, 2012. 110: E7.
84. Ouzzane, A., *et al.* Ureteral and multifocal tumours have worse prognosis than renal pelvic tumours in urothelial carcinoma of the upper urinary tract treated by nephroureterectomy. *Eur Urol*, 2011. 60: 1258.
85. Chromecki, T.F., *et al.* The impact of tumor multifocality on outcomes in patients treated with radical nephroureterectomy. *Eur Urol*, 2012. 61: 245.
86. Williams, A.K., *et al.* Multifocality rather than tumor location is a prognostic factor in upper tract urothelial carcinoma. *Urol Oncol*, 2013. 31: 1161.
87. Sundi, D., *et al.* Upper tract urothelial carcinoma: impact of time to surgery. *Urol Oncol*, 2012. 30: 266.
88. Gadzinski, A.J., *et al.* Long-term outcomes of immediate versus delayed nephroureterectomy for upper tract urothelial carcinoma. *J Endourol*, 2012. 26: 566.
89. Waldert, M., *et al.* A delay in radical nephroureterectomy can lead to upstaging. *BJU Int*, 2010. 105: 812.
90. Lee, J.N., *et al.* Impact of surgical wait time on oncologic outcomes in upper urinary tract urothelial carcinoma. *J Surg Oncol*, 2014. 110: 468.

91. Berod, A.A., *et al.* The role of American Society of Anesthesiologists scores in predicting urothelial carcinoma of the upper urinary tract outcome after radical nephroureterectomy: results from a national multi-institutional collaborative study. *BJU Int*, 2012. 110: E1035.
92. Martinez-Salamanca, J.I., *et al.* Prognostic role of ECOG performance status in patients with urothelial carcinoma of the upper urinary tract: an international study. *BJU Int*, 2012. 109: 1155.
93. Liu, J.Y., *et al.* Influence of body mass index on oncological outcomes in patients with upper urinary tract urothelial carcinoma treated with radical nephroureterectomy. *Int J Urol*, 2014. 21: 136.
94. Ehdaie, B., *et al.* Obesity adversely impacts disease specific outcomes in patients with upper tract urothelial carcinoma. *J Urol*, 2011. 186: 66.
95. Dalpiaz, O., *et al.* Validation of the pretreatment derived neutrophil-lymphocyte ratio as a prognostic factor in a European cohort of patients with upper tract urothelial carcinoma. *Br J Cancer*, 2014. 110: 2531.
96. Tanaka, N., *et al.* A multi-institutional validation of the prognostic value of the neutrophil-to-lymphocyte ratio for upper tract urothelial carcinoma treated with radical nephroureterectomy. *Ann Surg Oncol*, 2014. 21: 4041.
97. Mbeutcha, A., *et al.* Prognostic factors and predictive tools for upper tract urothelial carcinoma: a systematic review. *World J Urol*, 2016.
98. Fajkovic, H., *et al.* Prognostic value of extranodal extension and other lymph node parameters in patients with upper tract urothelial carcinoma. *J Urol*, 2012. 187: 845.
99. Roscigno, M., *et al.* Lymphadenectomy at the time of nephroureterectomy for upper tract urothelial cancer. *Eur Urol*, 2011. 60: 776.
100. Lughezzani, G., *et al.* A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. *Urology*, 2010. 75: 118.
101. Kikuchi, E., *et al.* Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. *J Clin Oncol*, 2009. 27: 612.
102. Novara, G., *et al.* Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. *Eur Urol*, 2010. 57: 1064.
103. Godfrey, M.S., *et al.* Prognostic indicators for upper tract urothelial carcinoma after radical nephroureterectomy: the impact of lymphovascular invasion. *BJU Int*, 2012. 110: 798.
104. Colin, P., *et al.* Influence of positive surgical margin status after radical nephroureterectomy on upper urinary tract urothelial carcinoma survival. *Ann Surg Oncol*, 2012. 19: 3613.
105. Zigeuner, R., *et al.* Tumour necrosis is an indicator of aggressive biology in patients with urothelial carcinoma of the upper urinary tract. *Eur Urol*, 2010. 57: 575.
106. Seitz, C., *et al.* Association of tumor necrosis with pathological features and clinical outcome in 754 patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma: an international validation study. *J Urol*, 2010. 184: 1895.
107. Remzi, M., *et al.* Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. *BJU Int*, 2009. 103: 307.
108. Fritsche, H.M., *et al.* Macroscopic sessile tumor architecture is a pathologic feature of biologically aggressive upper tract urothelial carcinoma. *Urol Oncol*, 2012. 30: 666.
109. Otto, W., *et al.* Concomitant carcinoma *in situ* as an independent prognostic parameter for recurrence and survival in upper tract urothelial carcinoma: a multicenter analysis of 772 patients. *World J Urol*, 2011. 29: 487.
110. Wheat, J.C., *et al.* Concomitant carcinoma *in situ* is a feature of aggressive disease in patients with organ confined urothelial carcinoma following radical nephroureterectomy. *Urol Oncol*, 2012. 30: 252.
111. Youssef, R.F., *et al.* Prognostic effect of urinary bladder carcinoma *in situ* on clinical outcome of subsequent upper tract urothelial carcinoma. *Urology*, 2011. 77: 861.
112. Pieras, E., *et al.* Concomitant carcinoma *in situ* and tumour size are prognostic factors for bladder recurrence after nephroureterectomy for upper tract transitional cell carcinoma. *BJU Int*, 2010. 106: 1319.
113. Comperat, E., *et al.* Prognostic value of MET, RON and histoprognostic factors for urothelial carcinoma in the upper urinary tract. *J Urol*, 2008. 179: 868.
114. Scarpini, S., *et al.* Impact of the expression of Aurora-A, p53, and MIB-1 on the prognosis of urothelial carcinomas of the upper urinary tract. *Urol Oncol*, 2012. 30: 182.
115. Kosaka, T., *et al.* Expression of snail in upper urinary tract urothelial carcinoma: prognostic significance and implications for tumor invasion. *Clin Cancer Res*, 2010. 16: 5814.
116. Feng, C., *et al.* Predictive value of clinicopathological markers for the metachronous bladder cancer and prognosis of upper tract urothelial carcinoma. *Sci Rep*, 2014. 4: 4015.

117. Bagrodia, A., *et al.* Evaluation of the prognostic significance of altered mammalian target of rapamycin pathway biomarkers in upper tract urothelial carcinoma. *Urology*, 2014. 84: 1134.
118. Roupret, M., *et al.* Microsatellite instability as predictor of survival in patients with invasive upper urinary tract transitional cell carcinoma. *Urology*, 2005. 65: 1233.
119. Margulis, V., *et al.* Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. *J Urol*, 2010. 184: 453.
120. Favaretto, R.L., *et al.* Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non-organ confined disease in patients with upper tract urothelial carcinoma. *BJU Int*, 2012. 109: 77.
121. Cha, E.K., *et al.* Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. *Eur Urol*, 2012. 61: 818.
122. Yates, D.R., *et al.* Cancer-specific survival after radical nephroureterectomy for upper urinary tract urothelial carcinoma: proposal and multi-institutional validation of a post-operative nomogram. *Br J Cancer*, 2012. 106: 1083.
123. Seisen, T., *et al.* Postoperative nomogram to predict cancer-specific survival after radical nephroureterectomy in patients with localised and/or locally advanced upper tract urothelial carcinoma without metastasis. *BJU Int*, 2014. 114: 733.
124. Roupret, M., *et al.* Prediction of cancer specific survival after radical nephroureterectomy for upper tract urothelial carcinoma: development of an optimized postoperative nomogram using decision curve analysis. *J Urol*, 2013. 189: 1662.
125. Ku, J.H., *et al.* External validation of an online nomogram in patients undergoing radical nephroureterectomy for upper urinary tract urothelial carcinoma. *Br J Cancer*, 2013. 109: 1130.
126. Roupret, M., *et al.* A new proposal to risk stratify urothelial carcinomas of the upper urinary tract (UTUCs) in a predefinitive treatment setting: low-risk versus high-risk UTUCs. *Eur Urol*, 2014. 66: 181.
127. Seisen, T., *et al.* Risk-adapted strategy for the kidney-sparing management of upper tract tumours. *Nat Rev Urol*, 2015. 12: 155.
128. Yakoubi, R., *et al.* Radical nephroureterectomy versus endoscopic procedures for the treatment of localised upper tract urothelial carcinoma: a meta-analysis and a systematic review of current evidence from comparative studies. *Eur J Surg Oncol*, 2014. 40: 1629.
129. Seisen, T., *et al.* Oncologic Outcomes of Kidney-sparing Surgery Versus Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Systematic Review by the EAU Non-muscle Invasive Bladder Cancer Guidelines Panel. *Eur Urol*, 2016. 70: 1052.
130. Mandalapu, R.S., *et al.* Update of the ICUD-SIU consultation on upper tract urothelial carcinoma 2016: treatment of low-risk upper tract urothelial carcinoma. *World J Urol*, 2016.
131. Gadzinski, A.J., *et al.* Long-term outcomes of nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma. *J Urol*, 2010. 183: 2148.
132. Cutress, M.L., *et al.* Long-term endoscopic management of upper tract urothelial carcinoma: 20-year single-centre experience. *BJU Int*, 2012. 110: 1608.
133. Cutress, M.L., *et al.* Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. *BJU Int*, 2012. 110: 614.
134. Kondo, T., *et al.* Template-based lymphadenectomy in urothelial carcinoma of the upper urinary tract: impact on patient survival. *Int J Urol*, 2010. 17: 848.
135. Cornu, J.N., *et al.* Oncologic control obtained after exclusive flexible ureteroscopic management of upper urinary tract urothelial cell carcinoma. *World J Urol*, 2010. 28: 151.
136. Roupret, M., *et al.* Upper urinary tract transitional cell carcinoma: recurrence rate after percutaneous endoscopic resection. *Eur Urol*, 2007. 51: 709.
137. Jeldres, C., *et al.* Segmental ureterectomy can safely be performed in patients with transitional cell carcinoma of the ureter. *J Urol*, 2010. 183: 1324.
138. Colin, P., *et al.* Comparison of oncological outcomes after segmental ureterectomy or radical nephroureterectomy in urothelial carcinomas of the upper urinary tract: results from a large French multicentre study. *BJU Int*, 2012. 110: 1134.
139. Giannarini, G., *et al.* Antegrade perfusion with bacillus Calmette-Guerin in patients with non-muscle-invasive urothelial carcinoma of the upper urinary tract: who may benefit? *Eur Urol*, 2011. 60: 955.
140. Irie, A., *et al.* Intravesical instillation of bacille Calmette-Guerin for carcinoma *in situ* of the urothelium involving the upper urinary tract using vesicoureteral reflux created by a double-pigtail catheter. *Urology*, 2002. 59: 53.
141. Phe, V., *et al.* Does the surgical technique for management of the distal ureter influence the outcome after nephroureterectomy? *BJU Int*, 2011. 108: 130.

142. Roupret, M., *et al.* Oncological risk of laparoscopic surgery in urothelial carcinomas. *World J Urol*, 2009. 27: 81.
143. Ong, A.M., *et al.* Trocar site recurrence after laparoscopic nephroureterectomy. *J Urol*, 2003. 170: 1301.
144. Favaretto, R.L., *et al.* Comparison between laparoscopic and open radical nephroureterectomy in a contemporary group of patients: are recurrence and disease-specific survival associated with surgical technique? *Eur Urol*, 2010. 58: 645.
145. Ni, S., *et al.* Laparoscopic versus open nephroureterectomy for the treatment of upper urinary tract urothelial carcinoma: a systematic review and cumulative analysis of comparative studies. *Eur Urol*, 2012. 61: 1142.
146. Walton, T.J., *et al.* Oncological outcomes after laparoscopic and open radical nephroureterectomy: results from an international cohort. *BJU Int*, 2011. 108: 406.
147. Ariane, M.M., *et al.* Assessment of oncologic control obtained after open versus laparoscopic nephroureterectomy for upper urinary tract urothelial carcinomas (UUT-UCs): results from a large French multicenter collaborative study. *Ann Surg Oncol*, 2012. 19: 301.
148. Simone, G., *et al.* Laparoscopic versus open nephroureterectomy: perioperative and oncologic outcomes from a randomised prospective study. *Eur Urol*, 2009. 56: 520.
149. Adibi, M., *et al.* Oncological outcomes after radical nephroureterectomy for upper tract urothelial carcinoma: comparison over the three decades. *Int J Urol*, 2012. 19: 1060.
150. Aboumohamed, A.A., *et al.* Oncologic Outcomes Following Robot-Assisted Laparoscopic Nephroureterectomy with Bladder Cuff Excision for Upper Tract Urothelial Carcinoma. *J Urol*, 2015. 194: 1561.
151. Abe, T., *et al.* Outcome of regional lymphadenectomy in accordance with primary tumor location on laparoscopic nephroureterectomy for urothelial carcinoma of the upper urinary tract: a prospective study. *J Endourol*, 2015. 29: 304.
152. Kondo, T., *et al.* Possible role of template-based lymphadenectomy in reducing the risk of regional node recurrence after nephroureterectomy in patients with renal pelvic cancer. *Jpn J Clin Oncol*, 2014. 44: 1233.
153. Fradet, V., *et al.* Risk factors for bladder cancer recurrence after nephroureterectomy for upper tract urothelial tumors: results from the Canadian Upper Tract Collaboration. *Urol Oncol*, 2014. 32: 839.
154. O'Brien, T., *et al.* Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). *Eur Urol*, 2011. 60: 703.
155. Ito, A., *et al.* Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP Monotherapy Study Group Trial. *J Clin Oncol*, 2013. 31: 1422.
156. Fang, D., *et al.* Prophylactic intravesical chemotherapy to prevent bladder tumors after nephroureterectomy for primary upper urinary tract urothelial carcinomas: a systematic review and meta-analysis. *Urol Int*, 2013. 91: 291.
157. Audenet, F., *et al.* The role of chemotherapy in the treatment of urothelial cell carcinoma of the upper urinary tract (UUT-UCC). *Urol Oncol*, 2013. 31: 407.
158. Kaag, M.G., *et al.* Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. *Eur Urol*, 2010. 58: 581.
159. Lane, B.R., *et al.* Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. *Cancer*, 2010. 116: 2967.
160. Matin, S.F., *et al.* Incidence of downstaging and complete remission after neoadjuvant chemotherapy for high-risk upper tract transitional cell carcinoma. *Cancer*, 2010. 116: 3127.
161. Hellenthal, N.J., *et al.* Adjuvant chemotherapy for high risk upper tract urothelial carcinoma: results from the Upper Tract Urothelial Carcinoma Collaboration. *J Urol*, 2009. 182: 900.
162. Vassilakopoulou, M., *et al.* Outcomes after adjuvant chemotherapy in the treatment of high-risk urothelial carcinoma of the upper urinary tract (UUT-UC): results from a large multicenter collaborative study. *Cancer*, 2011. 117: 5500.
163. Leow, J.J., *et al.* A Systematic Review and Meta-analysis of Adjuvant and Neoadjuvant Chemotherapy for Upper Tract Urothelial Carcinoma. *Eur Urol*, 2014. 66: 529.
164. Birtle, A.J., *et al.* Time to define an international standard of postoperative care for resected upper urinary tract transitional cell carcinoma (TCC) - opening of the peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (POUT) Trial. *BJU Int*, 2012. 110: 919.
165. Jwa, E., *et al.* Adjuvant radiotherapy for stage III/IV urothelial carcinoma of the upper tract. *Anticancer Res*, 2014. 34: 333.

166. Ploussard, G., *et al.* Conditional survival after radical nephroureterectomy for upper tract carcinoma. *Eur Urol*, 2015. 67: 803.
167. Colin, P., *et al.* Risk stratification of metastatic recurrence in invasive upper urinary tract carcinoma after radical nephroureterectomy without lymphadenectomy. *World J Urol*, 2014. 32: 507.
168. Bagley, D.H., *et al.* Ureteroscopic laser treatment of upper urinary tract neoplasms. *World J Urol*, 2010. 28: 143.
169. Villa, L., *et al.* Early repeated ureteroscopy within 6-8 weeks after a primary endoscopic treatment in patients with upper tract urothelial cell carcinoma: preliminary findings. *World J Urol*, 2016. 34: 1201.

10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer

J.A. Witjes (Chair), E. Compérat, N.C. Cowan,
G. Gakis, V. Hernández, T. Le Bret, A. Lorch,
A.G. van der Heijden, M.J. Ribal
Guidelines Associates: M. Bruins, E. Linares Espinós,
M. Rouanne, Y. Neuzillet, E. Veskimäe

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) have prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Separate EAU guidelines documents are available addressing upper urinary tract tumours [1], non-muscle-invasive bladder cancer (TaT1 and carcinoma *in situ*) [2], and primary urethral carcinomas [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Guidelines Panel consists of an international multidisciplinary group of clinicians, including urologists, a pathologist, a radiologist and an oncologist.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/bladder-cancermuscle-invasive-and-metastatic/?type=panel>.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version.

Several scientific publications are available (the most recent paper dating back to 2016 [4]), as are a number of translations of all versions of the EAU MIBC Guidelines. All documents are accessible through the EAU website: <http://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU published its first guidelines on bladder cancer in 2000. This document covered both superficial (non-muscle-invasive) bladder cancer and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition its own guidelines, resulting in the first publication of the MIBC Guidelines in 2004. This 2017 document presents a limited update of the 2016 version.

1.4.2 Summary of changes

New relevant references have been identified through a structured assessment of the literature and incorporated in the various chapters of the 2017 EAU NMIBC Guidelines.

Key changes in the 2017 print are:

- Section 3.2.6 Gender - This section has been expanded with additional data.
- Section 5.1.4 Urinary cytology and urinary markers - This section has been expanded with additional data.
- Section 6.2.4 Prognostic markers - A new section has been included.
- Section 7.4.4.1 Preparations for surgery - A new section on pain management has been included as well as additional data on estimated glomerular filtration rate.
- Section 7.4.4.2.1 Ureterocutaneostomy - This section has been expanded with additional data.
- Table 7.6 Management of neobladder morbidity - Additional information has been added.
- Section 7.8.10 Role of immunotherapy - This is a new section.

1.4.2.1 Change in summary of evidence

7.8.11 Summary of evidence and recommendations for metastatic disease

7.8.11 Summary of evidence for metastatic disease	LE
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase-II trial.	2a

2. METHODS

2.1 Data identification

For the 2017 MIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive literature search, covering all sections of the MIBC Guideline was performed. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between July 1st 2015 and April 5th 2016. A total of 2,298 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <http://uroweb.org/guideline/bladder-cancer-muscle-invasive-andmetastatic/?type=appendices-publications>.

References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

No separate peer-review was done for the 2017 print of the MIBC Guidelines.

2.3 Future goals

Topics considered for inclusion in the 2018 update of the MIBC Guidelines:

- Diagnostics - haematuria

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in the male population worldwide, whilst it drops to 11th when both genders are considered [6]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [6]. In the European Union, the age-standardised incidence rate is 19.1 for men and 4.0 for women [6, 7]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [6, 7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [6, 7]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, also partly caused by the different methodologies used in the studies and the quality of data collection [8, 9].

The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [9, 10].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, carcinoma *in situ* [CIS]) or submucosa (stage T1). In younger patients (< 40) this percentage is even higher [11]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to T2-4 tumours [7, 8, 12].

3.2 Aetiology

3.2.1 Tobacco smoking

Tobacco smoking is the most well-established risk factor for BC, causing 50-65% of male cases and 20-30% of female cases [13]. A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias and confounding can be discounted with reasonable confidence [14].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [15]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer published between 1961 and 2003, and the pooled risk estimates for BC demonstrated a significant association for both current

and former smokers [16]. Recently, an increase in risk estimates for current smokers relative to never smokers has been described suggesting this could be due to changes in cigarette composition [13]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within one to four years of quitting smoking and 60% after 25 years of cessation [15]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women.

3.2.2 **Occupational exposure to chemicals**

Occupational exposure is the second most important risk factor for BC. Work-related cases accounted for 20-25% of all BC cases in several series and it is likely to occur in occupations in which dyes, rubbers, textiles, paints, leathers, and chemicals are used [17]. The risk of BC due to occupational exposure to carcinogenic aromatic amines is significantly greater after ten years or more of exposure; the mean latency period usually exceeds 30 years [18, 19]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [8, 20].

3.2.3 **Radiotherapy**

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks of 2-4 [21]. In a population-based cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy (BT), and EBRT-BT were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [22].

It has recently been proposed that patients who have received radiotherapy (RT) for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [23]. Nevertheless, since longer follow-up data are not yet available, and as BC requires a long period to develop, patients treated with radiation and with a long life-expectancy are at a higher risk of developing BC [23].

3.2.4 **Dietary factors**

Several dietary factors have been considered to be related to BC; however, the links remain controversial. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is an on-going multicentre cohort study designed to examine the association between diet, lifestyle, environmental factors and cancer. They found no links between BC and fluid intake, red meat, vegetable and fruit consumption, and only recently they have described an inverse association between dietary intake of flavonols and lignans and the risk of BC, in particular aggressive tumours [24].

3.2.5 **Bladder schistosomiasis and chronic urinary tract infection**

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean [25]. There is a well-established relationship between schistosomiasis and urothelial carcinoma of the bladder, which can progress to squamous cell carcinoma (SCC), however, a better control of the disease is decreasing the incidence of SCC of the bladder in endemic zones such as Egypt [26, 27].

Similarly, invasive SCC has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between BC and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of BC in patients with recurrent UTIs in some series. However, some of these results may be attributed to recall bias [28].

3.2.6 **Gender**

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival rates. A meta-analysis including nearly 28,000 patients shows that female gender was associated with a worse survival outcome (HR: 1.20; 95% CI: 1.09-1.32) compared to male gender after radical cystectomy (RC) [29]. This finding had already been presented in a descriptive Nation-Wide Analysis based on 27,773 Austrian patients. After their analysis the authors found that cancer-specific-survival (CSS) was identical for pT1-tumours in both sexes, while women had a worse CSS in both age cohorts (< 70 years and ≥ 70 years) with higher tumour stages [30]. However this higher mortality is questioned once both genders receive the same therapy. In the population-based study from the Ontario Cancer Registry analysing all patients with BC treated with cystectomy or radical RT between 1994 and 2008, no differences in overall survival (OS), mortality and outcomes were found between males and females following radical therapy [31].

A population-based study from the MarketScan databases suggests that a possible reason for worse survival in the female population may be that women experienced longer delays in diagnosis than men, as the differential diagnosis in women includes diseases that are more prevalent than BC [32].

Furthermore, differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated

with an increase in BC risk, even after adjustment for smoking status. This result suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC [33-35].

3.2.7 Genetic factors

There is growing evidence that genetic susceptibility factors and family association may influence the incidence of BC. The relationship between family history of cancer and risk of BC was examined in a Spanish BC study showing that family history of cancer in first-degree relatives was associated with an increased risk of BC; the association being stronger among younger patients. Shared environmental exposure was recognised as a potentially confounding factor [36]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [37].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [38, 39].

3.2.8 Summary of evidence and recommendations for epidemiology and risk factors

Summary of evidence	LE
Worldwide, bladder cancer is the 11 th most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of bladder cancer diagnosis have been identified.	3
Active and passive tobacco smoking continues to be the main risk factor, while the exposure-related incidence is decreasing.	2a
The increased risk of developing bladder cancer in patients undergoing external-beam radiotherapy (EBRT), brachytherapy (BT), or a combination of EBRT and BT, must be taken into account during patient follow-up. As bladder cancer requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed up closely.	3

Recommendations	GR
The principal preventable risk factor for MIBC is active and passive smoking.	B
Notwithstanding stricter regulations, workers should be informed about the potential carcinogenic effects of a number of recognised substances, duration of exposure, and latency periods. Protective measures should be recommended.	A

3.3 Pathology

3.3.1 Handling of transurethral resection and cystectomy specimens

In transurethral resection (TUR), a snap frozen specimen from the tumour and normal looking bladder wall should be taken, if possible. Separate specimens should be taken from the superficial and deep areas of the tumour and sent to the pathology laboratory separately, in case the outcome will impact on treatment decisions. If random biopsies of the flat mucosa are taken, each biopsy specimen of the flat mucosa should also be sent separately.

In RC, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen. In some circumstances this procedure can also be performed by the urologist. In a female cystectomy specimen, the length of the urethral segment removed *en bloc* with the specimen should be checked, preferably by the urological surgeon [40].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [41, 42]. It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area should be included.

It is compulsory to study the urethra, the ureters, the prostate in men and the radial margins [43]. In urethra-sparing cystectomy; the level of urethral dissection, completeness of the prostate, specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra, uterus and vaginal top (in women) should be inked and documented.

All lymph node (LN) specimens should be provided in their totality, in clearly labelled containers. In case of doubt, or adipose differentiation of the LN, the entire specimen is to be included. LNs should be counted and measured on slides, capsular extension and percentage of LN invasion should be reported as well as vascular embols [44, 45]. In the case of metastatic spread in the perivesical fat without real LN structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+.

A meta-analysis indicated that LN density is an independent predictor of clinical outcome (HR OS: 1.45; 95% CI: 1.11-1.90) [46].

Positive margins in the peripelvic fat tissue (soft tissue margins), should be inked by the pathologist for evaluation. Positive margins decrease CSS in cases of pN0M0 urothelial carcinomas [47].

In rare cases, fresh frozen sections may be helpful to determine treatment strategy. A recent study confirmed the reliability of fresh frozen sections of obturator LNs, but further studies are warranted to confirm these results [48].

3.3.2 Pathology of muscle-invasive bladder cancer

In MIBC all cases are high-grade urothelial carcinomas. For this reason, no prognostic information can be provided by grading MIBC [49]. However, identification of some morphological subtypes may be important for prognostic reasons and treatment decisions [50, 51]. Recently, an update of the World Health Organization (WHO) grading was published [52] however, the data presented in these guidelines are based on the 2004 WHO classification [53]. Currently the following differentiations are used:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular differentiation [54, 55];
3. micropapillary and microcystic urothelial carcinoma;
4. nested variant [56] (including large nested variety);
5. lymphoepithelioma;
6. plasmocytoid, giant cell, signet ring, diffuse, undifferentiated;
7. some urothelial carcinomas with trophoblastic differentiation;
8. small-cell carcinomas [57];
9. sarcomatoid carcinomas.

3.3.3 Recommendations for the assessment of tumour specimens

Recommendations	GR
Record the depth of invasion (categories pT2a and pT2b, pT3a and pT3b or pT4).	A*
Record margins with special attention paid to the radial margin, prostate, ureter, urethra and peritoneal fat and uterus and vaginal top.	
Record the number of lymph nodes (LNs) and number of positive LNs.	
Record lymphatic or blood vessel invasion and extranodal extension.	
Record the presence of carcinoma <i>in situ</i> .	

*Upgraded following panel consensus.

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) classification (2017, 8th edition) is recommended [58]. Blood and lymphatic vessel invasion and LN infiltration have an independent prognostic significance [59]. It seems that the pN category is closely related to the number of LNs studied by the pathologist [58]. New prognostic markers are under study (see Section 6.2.4 Prognostic Markers).

4.2 Tumour, node, metastasis classification

The TNM classification of malignant tumours is the method most widely used to classify the extent of cancer spread [50-52, 58, 60] (Table 4.1).

Table 4.1: TNM classification of urinary bladder cancer [58]

T - Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : “flat tumour”
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	microscopically
T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in a common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

5.1.1 Symptoms

Painless haematuria is the most common presenting complaint. Other clinical signs include urgency, dysuria, increased frequency, and in more advanced tumours, pelvic pain and symptoms related to urinary tract obstruction.

5.1.2 Physical examination

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after transurethral resection of the bladder (TURB), to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [61, 62]. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), some caution is suggested with the interpretation of bimanual examination [63].

5.1.3 Bladder imaging

Patients with a bladder mass identified by any diagnostic imaging technique should undergo cystoscopy, biopsy and/or resection for histopathological diagnosis and staging.

5.1.4 Urinary cytology and urinary markers

Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours (LE: 3) and is a useful indicator in cases of high-grade malignancy or CIS.

However, positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract. Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or

intravesical instillations, but for experienced readers, specificity exceeds 90% [64, 65] (LE: 2b). However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [66].

A standardised reporting system redefining urinary cytology diagnostic categories was published in 2016 by the Paris Working Group [67]:

- Adequacy of urine specimens (Adequacy);
- Negative for high-grade urothelial carcinoma (Negative);
- Atypical urothelial cells (AUC);
- Suspicious for high-grade urothelial carcinoma (Suspicious);
- High-grade urothelial carcinoma (HGUC);
- Low-grade urothelial neoplasia (LGUN).

5.1.5 **Cystoscopy**

Ultimately, the diagnosis of BC is made by cystoscopy and histological evaluation of resected tissue. In general, cystoscopy is initially performed in the office using a flexible instrument. If a bladder tumour has been visualised unequivocally in earlier imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), diagnostic cystoscopy may be omitted and the patient can proceed directly to TURB for histological diagnosis. Currently, there is no evidence for the role of photodynamic diagnosis (PDD) in the standard diagnosis of invasive BC.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of any mucosal abnormalities. The use of a bladder diagram is recommended.

The use of PDD could be considered if a T1 high-grade tumour is present, to identify associated CIS. Presence of CIS may lead to a modified treatment plan (see Section 7.1). Photodynamic diagnosis is highly sensitive for the detection of CIS, but in experienced hands, the rate of false-positive results may be similar to that with regular white-light cystoscopy [68].

5.1.6 **Transurethral resection of invasive bladder tumours**

The goal of TURB is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection biopsies.

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm in diameter) can be resected *en bloc*, where the specimen contains the complete tumour plus a part of the underlying bladder wall including muscle. Larger tumours need to be resected separately in parts, which includes the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable him/her to make a correct diagnosis. In cases in which RT is considered and CIS is to be excluded, PDD can be used [69].

The involvement of the prostatic urethra and ducts in men with bladder tumours has been reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, in the presence of bladder CIS, and in multiple tumours [70, 71] (LE: 3). Involvement of the prostatic urethra can be determined either at the time of primary TURB or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative-predictive value and is more accurate [72-74].

5.1.7 **Second resection**

In the case of high-grade non-muscle-infiltrative tumour, residual disease is observed in 33-53% of patients [75-81]. In order to reduce the risk of understaging [76, 77], a second TURB resection is often required to determine the future treatment strategy.

Diagnosis of urethral tumour before cystectomy or positive urethral frozen section leads to urethrectomy and therefore excludes neobladder reconstruction. If indicated, in males, urethral frozen section has to be performed on the cystoprostatectomy specimen just below the verumontanum bladder neck and on the inferior limits of the bladder neck for females.

5.1.8 **Concomitant prostate cancer**

Prostate cancer is found in 25-46% of patients undergoing cystectomy for BC [82, 83]. The impact on survival is unknown but the impact on surgical treatment is limited.

5.1.9 Summary of evidence and specific recommendations for the primary assessment of presumably invasive bladder tumours

(For general information on the assessment of bladder tumours, see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]).

Summary of evidence	LE
Currently, treatment decisions cannot be based on molecular markers.	3

Recommendations	GR
During cystoscopy, describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Take a biopsy of the prostatic urethra for cases of bladder neck tumour, when bladder carcinoma <i>in situ</i> is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	C
Take a biopsy at the time of the second resection, if no biopsy was taken during the initial procedure.	C
In women undergoing subsequent orthotopic neobladder construction, obtain procedural information (including histological evaluation) of the bladder neck and urethral margin, either prior to or at the time of cystoscopy.	C
Specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen in the pathological report.	C

5.2 Imaging for staging of MIBC

The treatment and prognosis of MIBC is determined by tumour stage and grade [84, 85]. In clinical practice, CT and MRI are the imaging techniques used. The purpose of using imaging for staging MIBC is to determine prognosis and provide information to assist treatment selection. Tumour staging must be accurate to ensure that the correct choice of treatment is made. Imaging parameters required for staging MIBC are:

- extent of local tumour invasion;
- tumour spread to LNs;
- tumour spread to the upper urinary tract (UUT) and other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands).

5.2.1 Local staging of MIBC

Both CT and MRI may be used for assessment of local invasion, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 vs. T3a) [86]. The principal aim of CT and MRI is therefore to detect T3b disease, or higher.

5.2.1.1 MRI for local staging of invasive bladder cancer

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT, but poorer spatial resolution. In studies performed before the availability of multidetector CT, MRI was reported as more accurate in local assessment. The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). These values were 10-33% (mean 19%) higher than those obtained with CT [87]. Dynamic contrast-enhanced (DCE) MRI may help to differentiate bladder tumour from surrounding tissues or evaluate post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall, due to neovascularisation [88-90].

In 2006, a link was established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), which may result in fatal or severely debilitating systemic fibrosis. Patients with impaired renal function are at risk of developing NSF and the non-ionic linear gadolinium-based contrast agents should be avoided (gadodiamide, gadopentetate dimeglumine and gadoversetamide). A stable macrocyclic contrast agent should be used (gadobutrol, gadoterate meglumine or gadoteridol). Contrast-enhanced CT using iodinated contrast media should be considered as an alternative [91] (LE: 4).

5.2.1.2 CT imaging for local staging of MIBC

The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages from Ta to T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% [92] and increases with more advanced disease [93].

5.2.2 **Imaging of lymph nodes in MIBC**

Assessment of LN metastases based solely on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detection of LN metastases is low (48-87%). Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of LN metastases in a variety of primary pelvic tumours [94-99]. Pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, detected by CT or MRI, should be regarded as pathologically enlarged [100, 101]. Currently, there is no evidence supporting the routine use of positron emission tomography (PET) in the nodal staging of BC, although the method has been evaluated with varying results in small prospective trials [102-105].

5.2.3 **Upper urinary tract urothelial carcinoma**

Excretory-phase CT urography is the imaging technique with the highest diagnostic accuracy for upper urinary tract urothelial carcinoma (UTUC) and has replaced conventional intravenous urography and US as the first-line imaging test for investigating high-risk patients [106]. The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 with a specificity from 0.93 to 0.99, depending on the technique used [107-114]. Attention to technique is therefore important for optimal results.

For UTUC detected by CT urography, a biopsy for histopathological confirmation of diagnosis is recommended to eliminate false-positive results and to provide information regarding the grade of the tumour to aid in the choice of treatment [108, 109, 115-117]. The biopsy is usually performed endoscopically.

5.2.4 **Distant metastases at sites other than lymph nodes**

Prior to any curative treatment, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect lung [118] and liver metastases [119], respectively. Bone and brain metastases are rare at the time of presentation of invasive BC. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases [120, 121]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [122, 123] (LE: 2b).

5.2.5 **Future developments**

Evidence is accruing in the literature suggesting that fluorodeoxyglucose (FDG)-PET/CT might have potential clinical use for staging metastatic BC [124, 125], but there is no consensus as yet. The results of further trials are awaited before a recommendation can be made. Recently, the first study was published showing the superior feasibility of diffusion-weighted imaging (DWI) over T2-weighted and DCE MRI for assessing the therapeutic response to induction chemotherapy against MIBC [126]. The high specificity of DWI indicates that it is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Results from prospective studies are awaited.

5.2.6 **Summary of evidence and recommendations for staging in muscle-invasive bladder cancer**

Summary of evidence	LE
Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.	2b
There are currently insufficient data on the use of diffusion-weighted imaging (DWI) and fluorodeoxyglucose- positron emission tomography/computed tomography (FDG-PET/CT) in MIBC to allow a recommendation to be made.	

Recommendations	GR
In patients with confirmed MIBC, use computed tomography (CT) of the chest, abdomen and pelvis as the optimal form of staging. Include excretory-phase CT urography for complete examination of the upper urinary tract.	B
Diagnose upper urinary tract urothelial carcinoma (UTUC) using excretory-phase CT urography rather than magnetic resonance (MR) urography as excretory-phase CT urography has greater diagnostic accuracy and is associated with less cost, and greater patient acceptability.	C
Use MR urography when CT urography is contraindicated for reasons related to contrast administration or radiation dose.	C
Perform endoscopically-guided biopsy for histopathological confirmation of pre-operative diagnosis of UTUC.	C
Use CT or magnetic resonance imaging (MRI) for staging locally advanced or metastatic disease in patients in whom radical treatment is considered.	B
Use CT to diagnose pulmonary metastases. CT and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen.	C

6. PROGNOSIS

6.1 Introduction

The treatment and prognosis for MIBC is mainly determined by tumour and nodal stage [85]. The pathological report will inform on histological type, lymphovascular invasion, presence of CIS, positive margins and extranodal extension. In clinical practice, CT and MRI are the imaging techniques used.

6.2 MIBC and comorbidity

Complications related to RC may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for RC [127-129].

Advanced age has been identified as a risk factor for complications of RC, although chronological age is less important than biological age. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [130]. Female gender, an increased body mass index (BMI) and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [131].

Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal complications and a decrease of recurrence-free and OS after RC [132, 133]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

6.2.1 Evaluation of comorbidity

Rochon *et al.* have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [134]. The evaluation helps to identify the medical conditions likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [135].

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman *et al.*, who have demonstrated an association between comorbidity and adverse pathological and survival outcome following RC [136]. Similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality in a population-based competing risk analysis of > 11,260 patients from the Surveillance, Epidemiology, and End Results (SEER) registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased CSS [137]. Stratifying elderly patients according to their risk-benefit profile using a multidisciplinary approach will help to select patients most likely to benefit from radical surgery and to optimise treatment outcomes [138]. Unfortunately, most series evaluating RC do not include indices of comorbidity in the patient evaluation.

6.2.2 Comorbidity scales, anaesthetic risk classification and geriatric assessment

A range of comorbidity scales has been developed [139]; six of which have been validated [140-145] (LE: 3). The Charlson Comorbidity Index (CCI) ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners based on patients' medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for peri-operative mortality [146, 147], overall mortality [148], and cancer-specific mortality [149-152]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [153]. The age-

adjusted CCI (Table 6.1) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [154].

Table 6.1: Calculation of the Charlson Comorbidity Index

Number of points	Conditions
1 point	50-60 years
	Myocardial infarction
	Heart failure
	Peripheral vascular insufficiency
	Cerebrovascular disease
	Dementia
	Chronic lung disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2 points	61-70 years
	Hemiplegia
	Moderate to severe kidney disease
	Diabetes with organ damage
	Tumours of all origins
3 points	71-80 years
	Moderate to severe liver disease
4 points	81-90 years
5 points	> 90 years
6 points	Metastatic solid tumours
	AIDS

Interpretation

Health assessment of oncology patients must be supplemented by measuring their activity level. Extermann *et al.* have shown that there is no correlation between morbidity and competitive activity level [155]. The Eastern Cooperative Oncology Group (ECOG) PS scores and Karnofsky index have been validated to measure patient activity [156] (LE: 3). Performance score is correlated with patient OS after RC [151] and palliative chemotherapy [157-159].

1. Calculate Charlson Comorbidity Score or Index = i
 - a. Add comorbidity score to age score
 - b. Total denoted as 'i' in the Charlson Probability calculation (see below). i = sum of comorbidity score to age score
2. Calculate Charlson Probability (10-year mortality = Y)
 - a. Calculate $Y = 10^{(i \times 0.9)}$
 - b. Calculate $Z = 0.983^Y$ (where Z is the 10-year survival)

According to a consensus conference of the National Institutes of Health, the aim of the Standardized Geriatric Assessment (SGA) is to discover, describe and explain the many problems of elderly people, to catalogue their resources and strengths, to assess individual service needs, and to develop a co-ordinated plan of care. The SGA can be carried out by means of several protocols. These protocols differ in the completeness of diagnostic research. The most complete protocol is the Comprehensive Geriatric Assessment (CGA) [160] which is tailored to the care of cancer patients [161]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced BC [162].

6.2.3 Summary of evidence and recommendations for comorbidity scales

Summary of evidence	LE
Chronological age is of limited relevance.	3
A comorbidity score developed in particular for the assessment of patients diagnosed with bladder cancer would be helpful.	3

Recommendations	GR
Base the decision on bladder-sparing treatment or radical cystectomy in elderly/geriatric patients with invasive bladder cancer on tumour stage and comorbidity.	B
Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists (ASA) score should not be used in this setting (see section 7.4.4.1).	B

6.2.4 Prognostic markers

6.2.4.1 Tumour location

Location of the tumour at the bladder trigone has shown to be associated with an increased likelihood (OR 1.83 95% CI: 1.11-2.99) of nodal metastasis and decreased survival (OR 1.68; 95% CI: 1.11-2.55) [84].

6.2.4.2 Molecular markers

The performance of current commercially available pathological prognostic markers points to the relevance of including molecular prognostic markers into clinical practice [163], but so far very few studies have addressed this topic. At present, insufficient evidence exists to recommend the standard use of prognostic marker p53 in high-risk muscle-invasive disease, as it will not yield sufficient data upon which to base treatment in an individual patient [164].

Recent publications demonstrated four main molecular groups of BC:

- basal BC with the basal and claudin low-type group;
- luminal BC with luminal and p53-like subtype.

The basal group, which can have sarcomatoid aspects and shows an over-expression of epidermal growth factor receptor 3 (EGFR3), is chemosensitive, the luminal type displays an over-expression of fibroblast growth factor receptor 3 (FGFR3), epidermal growth factor receptor (ERBB2[↑] and ERBB3), and is chemotherapy resistant [50, 51, 165].

In 2014, the Cancer Genome Atlas (TCGA) project in BC reported on the integrated genomic analysis of the first 131 MIBC patients, identifying genes that are mutated in a significant proportion of BCs, several of which were not previously reported [166]. Profiling studies have also reported on validated biomarker panels that predict prognosis and can be used to identify patients who may benefit from more aggressive therapy [167]. In the coming years, expanding knowledge of BC carcinogenesis may change our management of the disease.

7. DISEASE MANAGEMENT

7.1 Treatment failure of non-muscle invasive bladder cancer

7.1.1 High-risk non-muscle-invasive urothelial carcinoma

The recurrence and progression rate of non-muscle invasive BC (NMIBC) strongly correlates with the factors as described in the European Organisation for Research and Treatment of Cancer (EORTC) risk calculator [168]. According to this calculator, the risk of progression after five years is 45% for high-risk tumours. In 2015, however, the EORTC group presented new nomograms based on two large phase III trials with a median follow up of 7.4 years. With one to three years of maintenance bacillus Calmette-Guérin (BCG), the risk for progression at five years was much lower: 19.3% for T1G3 tumours [169].

Meta-analyses have demonstrated that BCG-therapy prevents the risk of tumour recurrence [170] and the risk of tumour progression [171, 172] but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy [171-173]. The EAU NMIBC Guidelines present data supporting cystectomy in selected patients with NMIBC.

Large cystectomy series show a risk of an understaging error in TaT1 tumours of 35-62%. This may be caused by the presence of persisting or recurrent tumours due to omission of a second TURB or re-TURB, and the absence of neoadjuvant therapy [174-176]. Second TURB identifies upstaging to > T2 tumours in 10-20% of patients [177, 178].

Progression to MIBC significantly decreases CSS. In a review of nineteen trials including 3,088 patients, CSS after progression from NMIBC to MIBC was 35%, which is significantly worse compared to patients with MIBC without a history of NMIBC. This underlines the need to recommend early radical treatment, such as RC, in case of intravesical therapy failure [2, 179, 180].

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate RC to patients with non-muscle-invasive tumour who are at highest risk of progression [168, 181-183]. Risk factors are any of the following:

- T1 tumours;
- high-grade/G3 tumours;
- CIS;
- multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all conditions must be presented in this point).

Subgroup of highest-risk tumours:

- T1G3/high-grade associated with concurrent bladder CIS;
- multiple and/or large T1G3/HG and/or recurrent T1G3/high-grade;
- T1G3/high-grade with CIS in the prostatic urethra;
- unusual histology of urothelial carcinoma;
- lymphovascular invasion;
- BCG failures.

Although the percentage of patients with primary TaT1 tumours and the indication for cystectomy in TaT1 tumours is not specified in large cystectomy series, the ten-year recurrence-free survival rate is 80% and similar to that of TURB and BCG maintenance therapy [2, 175, 184, 185] (LE: 3).

Radical cystectomy is also strongly recommended in patients with BCG-refractory tumours, defined in the NMIBC guideline as:

- whenever muscle-invasive tumour is detected during follow-up;
- if high-grade, non-muscle-invasive papillary tumour is present at three months;
- if CIS (without concomitant papillary tumour) is present at both three and six months;
- if high-grade tumour appears during BCG therapy [186];
- high-grade recurrence after BCG (recurrence of high-grade/grade 3 [WHO 1973/2004] tumour after completion of BCG maintenance, despite an initial response).

Patients with disease recurrence within two years of initial TURB plus BCG therapy have a better outcome than patients who already have muscle-invasive disease, indicating that cystectomy should be performed at first recurrence, even in non-muscle-invasive disease [187] (LE: 3; GR: C).

There are now several bladder-preservation strategies available; immunotherapy, chemotherapy, device-assisted therapy, and combination therapy [188]. However, experience is limited and treatments other than RC must be considered oncologically inferior at the present time [188].

7.1.2 **Recommendations for treatment failure of non-muscle-invasive bladder cancer**

Recommendations	GR
Consider immediate radical treatment in all T1 tumours at high risk of progression (i.e., high grade, multifocality, carcinoma <i>in situ</i> , and tumour size, as outlined in the EAU Guidelines for Non-muscle-invasive Bladder Cancer).	C
Offer radical treatment to all T1 patients failing intravesical therapy.	B

7.2 **Neoadjuvant chemotherapy**

7.2.1 **Introduction**

The standard treatment for patients with MIBC is RC. However, RC only provides five-year survival in about 50% of patients [176, 189-192]. To improve these results, neoadjuvant chemotherapy (NAC) has been used since the 1980s [193, 194].

There are many advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with resectable muscle-invasive urothelial carcinoma of the bladder and cNOMO disease:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of *in-vivo* chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients might respond to NAC and reveal a favourable pathological status, determined mainly by achieving pT0, pN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [195, 196], although published studies on the negative effect of delayed cystectomy only include chemo-naïve patients. There are no trials indicating that delayed surgery, due to NAC, has a negative impact on survival.

- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial the same distribution of grade 3-4 post-operative complications was seen in both treatment arms [197]. In the combined Nordic trials (n = 620), NAC did not have a major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm, 71% received all three chemotherapy cycles [198].
- Clinical staging using bimanual palpation, CT or MRI may often result in over- and understaging and have a staging accuracy of only 70% [199, 200]. Overtreatment is a possible negative consequence.
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin combination chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been fully tested in a neoadjuvant setting [197, 201-213].

7.2.2 *The role of imaging and biomarkers to identify responders*

Data from small imaging studies, aiming to identify responders in patients treated with NAC, suggest that response after two cycles of treatment is related to outcome. So far, neither PET, CT, nor conventional MRI or DCE MRI can accurately predict response [214-217]. In addition, the definition of stable disease after two cycles of NAC is still undefined. To identify progression during NAC, imaging is being used in many centres, notwithstanding the lack of supporting evidence.

For responders to NAC, especially in those with a complete response (pT0 N0), treatment has a major positive impact on OS [218]. The overtreatment of non-responders and patients in the non-target population (i.e. patients without micrometastatic disease) are major drawbacks. Pre-operative identification of responders based on molecular tumour profiling in TURB specimens might guide the use of NAC [219, 220] (see Section 7.8.12 - Biomarkers).

7.2.3 *Summary of available data*

Several randomised phase III trials addressed the potential survival benefit of NAC administration, with conflicting results [197, 201-210, 221-226]. The main differences in trial designs were the type of chemotherapy (i.e. single-agent cisplatin or combination chemotherapy) and the number of cycles provided. Patients had to be fit for cisplatin. Since these studies differed considerably for patient numbers, patient characteristics (e.g. clinical T-stages included) and the type of definitive treatment offered (cystectomy and/or RT), pooling of results was not possible.

Three meta-analyses were undertaken to establish if NAC prolongs survival [211-213]. In the most recent meta-analysis, published in 2005 [213], with updated patient data from 11 randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC. The results of this analysis confirmed the previously published data and showed a 5% absolute improvement in survival at five years.

The Nordic combined trial showed an absolute benefit of 8% survival at five years and 11% in the clinical T3 subgroup, translating into nine patients needed to treat [198]. Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [211, 213]; the regimens tested were methotrexate, vinblastine, adriamycin plus cisplatin (MVA(E)C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin and methotrexate (CM), cisplatin/adriamycin, cisplatin/5-fluorouracil (5-FU), and carboplatin, methotrexate, vinblastine (CarboMV).

More modern chemotherapeutic regimens such as gemcitabine/cisplatin have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) in the most recent retrospective series and pooled data analyses, but have not been used in randomised controlled trials (RCTs) [227-230]. The updated analysis of the largest randomised phase III trial [201] with a median follow-up of eight years confirmed previous results and provided some additional interesting findings:

- 16% reduction in mortality risk;
- improvement in ten-year survival from 30% to 36% with neoadjuvant CMV;
- benefit with regard to distant metastases;
- no benefit for locoregional control and locoregional disease-free survival, with the addition of neoadjuvant CMV independent of the definitive treatment.

The presence of micrometastases is postulated to be lower in smaller tumours (T2) compared to more extensive tumours (T3b-T4b). T4 stage tumours are prone to a higher degree of clinical understaging because macrometastatic nodal deposits are detected more often in post-cystectomy specimens [198]. Data support the use of NAC in the T2b-T3b tumour subgroup (former classification T3), and has shown a modest, but substantial, improvement in long-term survival as well as significant downstaging [218].

7.2.4 Summary of evidence and recommendations for neoadjuvant chemotherapy

Conclusions	LE
Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.	3
Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (OS) (5-8% at five years).	1a
Neoadjuvant treatment of responders and especially patients who show complete response (pT0 N0) has a major impact on OS.	2
Currently, no tools are available to select patients who have a higher probability of benefitting from neoadjuvant chemotherapy (NAC). In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for NAC and differentiate responders from non-responders.	

Recommendations	GR
Offer neoadjuvant chemotherapy (NAC) for T2-T4a, cN0M0 bladder cancer. In this case, always use cisplatin-based combination therapy.	A
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	A

7.3 Pre- and post-operative radiotherapy in muscle-invasive bladder cancer

7.3.1 Post-operative radiotherapy

There are only very limited, old, data on adjuvant RT after RC. However, advances in targeting, and reducing the damage to surrounding tissue, may yield better results in the future [231]. A recent RCT in 100 patients, comparing pre-operative vs. post-operative RT and RC, showed comparable OS, DFS and complication rates [232]. Approximately half of these patients had urothelial cancer (UC), while the other half had SCC. In locally advanced BC (T3-T4, N0/N1, M0), the local recurrence rate seems to decrease with post-operative RT [233].

7.3.2 Pre-operative radiotherapy

7.3.2.1 Retrospective studies

Older data and retrospective studies alone cannot provide an evidence base for modern guideline recommendations due to the major study limitations, which include concomitant chemotherapy and differences between surgery and RT. This conclusion was supported by a 2003 systemic review [234]. A retrospective study from 2015 [235] did show a decreased cause-specific mortality and overall mortality for pre-operative RT in clinical T2b and T3 patients only. Another recent retrospective study with pre-operative RT in clinical T1-3 tumours showed that downstaging to T0 tumours occurs in > 50% of the irradiated patients, as compared to < 10% of patients without having received pre-operative RT [236]. Additionally, downstaging resulted in a longer progression-free survival (PFS).

7.3.2.2 Randomised studies

Six randomised studies have been published so far, investigating pre-operative RT, although all are from several decades ago. In the largest trial, pre-operative RT at a dose of 45 Gy was used in patients with muscle-invasive tumours resulting in a significant increase in pathological complete response (pCR) (9% to 34%) in favour of pre-operative RT, which was also a prognostic factor for survival [237]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in \geq T3 tumours [238, 239]. Two other small trials confirmed downstaging after pre-operative RT [240, 241].

A meta-analysis of the five randomised trials showed a difference in five-year survival of (OR: 0.71; 95% CI: 0.48-1.06) in favour of pre-operative RT [242]. However, the meta-analysis was potentially biased by the patients in the data from largest trial who were not given the planned treatment. When the largest trial was excluded, the OR became 0.94 (95% CI: 0.57-1.55), which is not significant.

7.3.3 Summary of evidence and recommendations for pre- and post-operative radiotherapy

Summary of evidence	LE
No data exist to support that pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer (MIBC) increases survival.	2a
Pre-operative RT for operable MIBC, using a dose of 45-50 Gy in fractions of 1.8-2 Gy, results in downstaging after four-six weeks.	2
Limited high-quality evidence supports the use of pre-operative RT to decrease the local recurrence of MIBC after radical cystectomy.	3

Recommendations	GR
Do not offer pre-operative radiotherapy (RT) to improve survival.	A
Offer pre-operative RT for operable MIBC since it can result in tumour downstaging after four to six weeks.	C

7.4 Radical surgery and urinary diversion

7.4.1 Removal of the tumour-bearing bladder

7.4.1.1 Introduction

Radical cystectomy is the standard treatment for localised MIBC in most Western countries [176, 243]. Recent interest in patients' quality of life (QoL) has promoted the trend toward bladder-preserving treatment modalities, such as radio- and/or chemotherapy (see Sections 7.2 and 7.6). Performance status (PS) and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a multivariate analysis [149]. The analysis found an association between comorbidity and adverse pathological- and survival outcome following RC [149]. Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [155].

Controversy remains regarding age, RC and the type of urinary diversion. Cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged > 80 years [149]. The largest, retrospective, single-institution study on cystectomy to date found that patients aged > 80 years had increased post-operative morbidity, but not increased mortality. Although some patients successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion [244].

It is particularly important to evaluate functioning and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation (see Section 6.2) [245].

7.4.2 Timing and delay of cystectomy

Nielsen *et al.* reported that a delay of RC > 3 months in three American centres was not associated with a worse clinical outcome [246]. Ayres *et al.* investigated whether a delay > 3 months would have the same effect in the United Kingdom [247]. Initially they found, in agreement with Nielsen *et al.*, that cystectomy within 90 days of diagnosis had no effect on OS for MIBC (n = 955). However, analysis of T2 tumours showed a statistically significant survival benefit if patients had surgery within 90 days of diagnosis (n = 543; HR: 1.40; 95% CI: 1.10-1.79). A population-based study from the USA SEER database analysed patients who underwent a cystectomy between 1992 and 2001, also concluded that a delay of more than twelve weeks has a negative impact on outcome and should be avoided [248].

7.4.2.1 Indications

Traditionally, RC was recommended for patients with MIBC T2-T4a, N0-Nx, M0 [243]. Other indications include high risk and recurrent superficial tumours, BCG-resistant Tis, T1G3 (see Section 7.1), as well as extensive papillary disease that cannot be controlled with TURB and intravesical therapy alone.

Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-urothelial carcinoma (these tumours respond poorly to chemotherapy and RT). It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent visible haematuria (macrohaematuria) (see Section 7.5.1 - Palliative cystectomy).

When there are positive LNs, in the case of N1 involvement (metastasis in a single node in the true pelvis) orthotopic neobladder can still be considered, but not in N2 or N3 tumours [249].

7.4.3 **Radical cystectomy: technique and extent**

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs. Prostate-sparing cystectomy is an option in a subset of carefully selected patients with BC without involvement of the prostatic urethra and without prostate cancer. This procedure is oncologically safe with good functional results as long as it is performed in an experienced centre [250]. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs [251]. Controversies in evaluating the clinical significance of lymphadenectomy are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

Two important autopsy studies for RC have been performed so far. The first study showed that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal LNs. There was also a significant correlation between nodal metastases and concomitant distant metastases ($p < 0.0001$).

Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation [252]. The second autopsy study focused on the nodal yield when super-extended pelvic LN dissection (LND) was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [253]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional LNs have been shown to consist of all pelvic LNs below the bifurcation of the aorta [254-258]. Mapping studies have also found that skipping lesions at locations above the bifurcation of the aorta, without more distally located LN metastases, is rare [258, 259].

The extent of LND has not been established to date. Standard lymphadenectomy in BC patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes [260]. Extended lymphadenectomy includes all LNs in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the LN of Cloquet, as well as the area described for standard lymphadenectomy [260-264]. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery [265, 266].

In order to assess how and if cancer outcome is influenced by the extent of lymphadenectomy in patients with clinical N0M0 MIBC, a SR of the literature was undertaken [267]. Out of 1,692 abstracts retrieved and assessed, nineteen studies fulfilled the review criteria [260-264, 266, 268-280]. All five studies comparing LND vs. no LND reported a better oncological outcome for the LND group. Seven out of twelve studies comparing (super-)extended with limited or standard LND reported a beneficial outcome for (super)extended in at least a subset of patients which is in concordance with several other recently performed meta-analyses [281, 282]. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [266, 278]. Further data from on-going randomised trials on the therapeutic impact of the extent of lymphadenectomy are awaited.

It has been suggested that PFS as well as OS might be correlated with the number of LNs removed during surgery, although there are no data from RCTs on the minimum number of LNs that should be removed. Nevertheless, survival rates increase with the number of dissected LNs [283]. Removal of at least ten LNs has been postulated as sufficient for evaluation of LN status, as well as being beneficial for OS in retrospective studies [284-286]. In conclusion, extended LND might have a therapeutic benefit compared to less-extensive LND, but due to study bias, no firm conclusions can be drawn [267].

7.4.3.1 *Pelvic organ preservation techniques in men: oncological and functional outcomes*

Different approaches have been described to improve voiding and sexual function in patients undergoing RC for BC. No consensus exists regarding which approach preserves function best. Concern remains regarding the impact of "sparing-techniques" on oncological outcomes.

To determine the effect of sexual function-preserving cystectomy (SPC) on functional and oncological outcomes a SR was undertaken [287].

Four main types of sexual-preserving techniques have been described:

1. **Prostate sparing cystectomy:** part or the whole prostate is preserved including seminal vesicles, vas deferens and neurovascular bundles.
2. **Capsule sparing cystectomy:** the capsule or peripheral part of the prostate is preserved with adenoma

(including prostatic urethra) removed by TURP or *en bloc* with bladder. Seminal vesicles, vas deferens and neurovascular bundles are also preserved.

3. **Seminal sparing cystectomy:** seminal vesicles, vas deferens and neurovascular bundles are preserved.
4. **Nerve sparing cystectomy:** the neurovascular bundles are the only tissue left in place.

Out of 8,517 screened abstracts twelve studies recruiting a total of 1,098 patients (823 in the intervention group vs. 275 in the control group) were identified, including nine comparative studies (one RCT and two retrospective non-RCTs with matched pair design [250, 288-297] and three single-arm case series [298-300]. Sexual function-preserving cystectomy described included prostate-, capsule-, seminal vesicle- and nerve-sparing techniques. In the majority of cases, the open surgical approach was used and the urinary diversion of choice was an orthotopic neobladder. Median follow-up was longer than three years in nine studies, with three studies presenting results at a median follow-up longer than five years.

The majority of the studies included patients who were potent pre-operatively with organ-confined disease without tumour in the bladder neck and/or prostatic urethra. Prostate cancer was ruled out in all of the SPC techniques, except in those performing nerve-sparing cystectomy.

Oncological outcomes did not differ between groups in any of the comparative studies that measured local recurrence, metastatic recurrence, DSS and OS, at a median follow-up of three to five years. Local recurrence after SPC was commonly defined as any urothelial cancer (UC) recurrence below the iliac bifurcation within the pelvic soft tissue and ranged from 1.2-61.1% vs. 16-55% in the control group. Metastatic recurrence ranged from 0-33.3%.

For those techniques preserving prostatic tissue (prostate or capsule sparing) rates of incidental prostate cancer in the intervention group ranged from 0 to 15%. In no case, incidental prostate cancer with Gleason score ≥ 8 was reported.

Sexual outcomes were evaluated using validated-questionnaires (International Index of Erectile Function [IIEF], Erection Hardness Scale [EHS], Bladder Cancer Index [BCI]) in eight studies. Post-operative potency was significantly better in patients who underwent any type of sexual-preserving technique compared to conventional RC ($p < 0.05$), ranging 80-90%, 50-100% and 29-78% for prostate-, capsule- or nerve-sparing techniques, respectively. Data did not show superiority of any sexual-preserving technique.

Urinary continence, defined as the use of no pads in the majority of studies, ranged from 88 to 100% (day-time continence) and from 31-96% (night-time continence) in the prostate-sparing cystectomy patients. No major impact was shown with regard to continence rates for any of the three approaches.

The evidence base suggests that these procedures may yield better sexual outcomes than standard cystectomy without compromising oncological outcomes. However, the overall quality of the evidence was moderate, and hence if a sexual-preserving technique is offered, patients must be carefully selected, counselled and closely monitored.

7.4.3.1.1 Summary of evidence and recommendations for sexual-preserving techniques in men

Summary of evidence	LE
The majority of patients motivated to preserve their sexual function will benefit from sexual-preserving techniques.	2
None of the sexual-preserving techniques (prostate/capsule/seminal/nerve sparing) have shown to be superior and no particular technique can be recommended.	

Recommendations	LE	GR
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	2	B
Select patients based on: <ul style="list-style-type: none"> • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck. 	2	A
Do not offer sexual-preserving cystectomy as standard therapy for muscle-invasive bladder cancer.		C

7.4.3.2 Pelvic organ preservation techniques in women: oncological and functional outcomes

Sexual and voiding dysfunction in female patients is prevalent after RC and orthotopic neobladder. Patients' QoL has promoted the trend toward pelvic organ-preserving techniques. Better imaging modalities, increased knowledge of the function of the pelvic structures and improved surgical techniques has enabled less destructive methods for treating high-risk BC. These techniques involve preserving the neurovascular bundle, vagina, uterus or variations of any of the stated techniques.

A SR was conducted to evaluate the advantages and disadvantages of sexual-function preserving RC and orthotopic neobladder for female patients [301].

After screening 11,941 abstracts, fifteen studies recruiting a total of 874 patients were eligible for inclusion. Three papers had a matched pair study design, and the remainder of the included studies were retrospective surgical series with small case numbers and a high risk of selection bias favouring less advanced cancers.

Sexual outcomes were reported in seven studies with 167/194 patients (86%) having resumed sexual activity within six months post-operatively, with median patients' sexual satisfaction scores of 88.5%, ranging from 80% to 100%.

Survival outcomes were reported in seven studies on 197 patients, with a mean follow-up of between 12 and 132 months. At three and five year, CSS was 70-100% and OS was 65-100%. Positive surgical margins were reported in six studies, ranging from 0 to 13.7%. Local and metastatic recurrence rates were reported as ranging between 0-13% and 0-16.7%, respectively. Mean time to local recurrence was seven months.

Eleven studies reported continence outcomes. Overall daytime and nighttime continence was 58-100% and 42-100%, respectively. Overall self-catheterisation rate was 9.5-78%.

Although, this SR provides the best evidence currently available, including basically all reported cases, the data remains immature. Most studies were retrospective and non-comparative with small numbers of patients included, meaning that any estimates are uncertain and likely to be biased. Heterogeneity in outcome definition, measurement and reporting hampers the usefulness of the current evidence base. The overall risk of bias was high across all studies. However, for well-selected patients, sparing female reproductive organs during RC appears to be oncologically safe and provides improved functional outcomes.

7.4.3.2.1 Summary of evidence and recommendations for sexual-preserving techniques in women

Summary of evidence	LE
Data regarding pelvic organ-preserving radical cystectomy for female patients remain immature.	3

Recommendations	LE	GR
Offer sexual-preserving techniques to female patients motivated to preserve their sexual function since the majority will benefit.	3	C
Select patients based on: <ul style="list-style-type: none"> • organ-confined disease; • absence of tumour in bladder neck or urethra. 		C
Do not offer pelvic organ-preserving radical cystectomy for female patients as standard therapy for muscle-invasive bladder cancer.		C

7.4.3.3 Laparoscopic/robotic-assisted laparoscopic cystectomy

Due to data limitations, until recently, laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) were considered as investigational procedures for which no advantages could be shown as compared to open surgery. Most of the available studies suffered from patient selection bias (age, stage).

A number of new publications have become available (cut-off date for the literature search was Oct 1st, 2015), in particular on RARC; a SR [302], a consensus panel report [303], an RCT from the Memorial Sloan Kettering Cancer Center (MSKCC) group [304] a SR on oncologic and functional outcomes after RARC [305] and a retrospective review on the recurrence patterns after open radical cystectomy (ORC) and RARC [306]. Since there is a continuous flow of reports on RARC, this text section and the recommendations will be subject to significant updates in the coming years.

For the methodology of the SR we refer to the manuscript [302]. In short, out of 1,071 abstracts assessed, 105 studies were selected as meeting the inclusion criteria. Of the 105 papers 102 had a level of evidence of 4, and only three publications had a level of evidence of 2b.

For RARC with urinary diversion, the mean operative time was six to seven hours. Although the intracorporeal technique is more demanding, operating times are comparable, most likely reflecting more experience with the procedure. The operation time decreased over time, but remained longer than for ORC. The average operative time for ORC is listed as 297 minutes in the three higher quality RCTs, which still seems relatively long.

In the comparative studies, mean length of hospital stay for RARC decreases with time and experience, and is 1 to 1.5 days shorter as compared to ORC. In the RCT's however, operative time and length of hospital stay showed no significant difference for either procedure. Blood loss and transfusion rate favour RARC. Intraoperative, 30-day complication rate and mortality were similar for RARC and ORC, but complication grade and grade 3, 90-day, complication rates favoured RARC. Overall complication rates were reported as > 50% which illustrates that cystectomy and diversion remains major surgery. Complication rates did not change with time or experience.

A major limitation of this review is the low level of evidence of the included studies. Of the three RCT's, only one was adequately powered and there was no correction for baseline characteristics (selection bias). In some of the larger series in the review 59-67% of tumours are < pT2 tumours. In the largest RCT 91.5% were clinically < T2 and 71.7% pathologically < T2 [304] compared to a large series of ORC (n = 1,054) 47% of included patients had a < pT2 tumour [176].

The Pasadena Consensus Panel (a group of experts on RC, lymphadenectomy and urinary reconstruction) reached similar conclusions as the Novara review based on the same methodology and literature [303]. They presented similar outcomes comparing RARC and ORC for operative endpoints, pathological and intermediate oncological endpoints (positive surgical margins and LN yield), functional endpoints and complication outcomes. Additionally, RARC was associated with increased costs, although there are ergonomic advantages for the surgeon, as compared to laparoscopic radical cystectomy (LRC). For both techniques surgeons' experience and institutional volume strongly predicted outcome. According to the literature, proficiency is reached after 20-250 cases. However, the Pasadena Consensus Panel performed statistical modelling and came to the conclusion that 30 cases should be enough to achieve proficiency in RARC, but they also concluded that challenging cases (high BMI, post chemo- or RT, pelvic surgery, T4 or bulky tumours or positive nodes) should be performed by experienced robotic surgeons only. Experience is defined as a high volume centre, > 30 RARCs/year and experience in ORC.

In the only sufficiently powered RCT, comparing ORC (n = 58) vs. RARC (n = 60) and open diversion, the primary endpoint was an advantage in 90 days grade 2-5 complications for RARC [304]. Since the complication rates were similar (62% for RARC vs. 66% for ORC), the trial was closed after a planned interim analysis. Robotic-assisted radical cystectomy resulted in less blood loss but had a longer operative time and higher costs. Length of hospital stay, pathology, and QoL were similar. Limitations of this study are lack of long-term outcomes and limited experience in RARC as compared to ORC in this group of patients. A similar health-related QoL (HRQoL) was also found in an initial report of a prospective RCT comparing ORC and RARC [307]. Similar functional and oncological outcomes with five years follow up were also reported by Yuh *et al.* [305]. Ngyuyen *et al.* also reported that RARC was not an independent predictor of recurrence after surgery in a retrospective review of 383 consecutive patients [306].

Most reviewed series used extracorporeal reconstruction which leaves room for improvement.

Although an intracorporeal neobladder is a very complex robotic procedure [308] the choice for neobladder or cutaneous diversion, must not depend on the surgical approach.

For LRC, a recent review came to similar conclusions as described for RARC [308]. The review included sixteen eligible studies on LRC. As compared to ORC, LRC had a significantly longer operative time, fewer overall complications, blood transfusions and analgesic use, less blood loss and a shorter length of hospital stay. However, the review was limited by the inherent limitations of the included studies. Although this review also showed better oncological outcomes, these appeared comparable to ORC series in the largest LRC multicentre study to date [308].

7.4.3.3.1 Summary of evidence and recommendations for laparoscopic/robotic-assisted laparoscopic cystectomy

Summary of evidence	LE
Robot-assisted radical cystectomy (RARC) provides longer operative time (1-1.5 hours), major costs, but shorter length of hospital stay (1-1.5 days) and less blood loss compared to open radical cystectomy (ORC).	1
RARC series suffer from a significant stage selection bias as compared to ORC.	1
Grade 3, 90-day complication rate is lower with RARC.	2
Most endpoints, if reported, including intermediate term oncological endpoint and quality of life are not different between RARC and ORC.	2
Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.	2
Recommendations on how to define challenging patients and an experienced RARC surgeon are still under discussion.	3
The use of neobladder after RARC still seems under-utilised, and functional results of intracorporeally constructed neobladders should be studied.	4

Recommendations	GR
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	C
Select experienced centres, not specific techniques, both for RARC and ORC.	B
Beware of neobladder under-utilisation and outcome after RARC.	C

7.4.4 Urinary diversion after radical cystectomy

From an anatomical standpoint, three alternatives are currently used after cystectomy:

- abdominal diversion, such as an ureterocutaneostomy, ileal or colonic conduit, and various forms of a continent pouch;
- urethral diversion, which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder substitution);
- rectosigmoid diversions, such as uretero-(ileo-)rectostomy.

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix [309]. Several studies have compared certain aspects of HRQoL, such as sexual function, urinary continence and body image, in patient cohorts with different types of urinary diversion. However, further research is needed on pre-operative tumour stage and functional situation, socio-economic status, and time interval to primary surgery.

7.4.4.1 Preparations for surgery

The ASA score has been validated to assess the risk of post-operative complications prior to surgery. In the BC setting, ASA scores ≥ 3 are associated with major complications [132, 310], particularly those related to the type of urinary diversion (Table 7.4) [311]. However, the ASA score is not a comorbidity scale and should not be used as such.

Table 7.4: ASA score [312]

ASA	
1	No organic pathology, or patients in whom the pathological process is localised and does not cause any systemic disturbance or abnormality.
2	A moderate but definite systemic disturbance caused either by the condition that is to be treated or surgical intervention, or which is caused by other existing pathological processes.
3	Severe systemic disturbance from any cause or causes. It is not possible to state an absolute measure of severity, as this is a matter of clinical judgment.
4	Extreme systemic disorders that have already become an imminent threat to life, regardless of the type of treatment. Because of their duration or nature, there has already been damage to the organism that is irreversible.
5	Moribund patients not expected to survive 24 hours, with or without surgery.

In consultation with the patient, both an orthotopic neobladder and ileal conduit should be considered in case where reconstructive surgery exposes the patient to excessive risk (as determined by comorbidity and age).

Diagnosis of urethral tumour before cystectomy or positive urethral frozen section leads to urethrectomy and therefore excludes neobladder reconstruction. If indicated, in males, urethral frozen section has to be performed on the cystoprostatectomy specimen just under the verumontanum and on the inferior limits of the bladder neck for females.

When there are positive LNs, orthotopic neobladder can nevertheless be considered in the case of N1 involvement (metastasis in a single node in the true pelvis) but not for N2 or N3 tumours [313].

Oncological results after orthotopic neobladder substitution or conduit diversion are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with neobladder compared to those with conduits or continent cutaneous diversions [314].

For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the urinary diversion is constructed from gastrointestinal segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered [315]. Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary [316]. Bowel recovery time can be reduced by the use of early mobilisation and early oralisation, gastrointestinal stimulation with metoclopramide and chewing gum [317]. Patients treated according to the “fast tract”/ERAS (Early Recovery After Surgery) protocol have shown to score better on the emotional and physical functioning scores and suffer less from wound healing disorders, fever and thrombosis [318].

A cornerstone of the ERAS protocol is post-operative pain management which involves significantly reducing the use of opioids; offering opioids mainly as breakthrough pain medication. Instead of patient-controlled analgesia (PCA) and epidural opioids, most patients receive high-dose acetaminophen and/or ketorolac, starting intra-operatively. Patients on ERAS experience more pain as compared to patients on a traditional protocol (VAS 3.1 vs. 1.1, $p < 0.001$), but post-operative ileus decreased from 22% to 7.3% ($p = 0.003$) [319].

A multicentre randomised placebo-controlled trial showed that patients receiving alvimopan, a peripherally acting μ -opioid receptor antagonist, experienced quicker bowel recovery compared to patients receiving placebo [320]. However, this drug is, as yet, not approved in Europe.

Patients undergoing continent urinary diversion must be motivated to learn about their diversion and to be manually skilful in manipulating their diversion. Contraindications to more complex forms of urinary diversion include:

- debilitating neurological and psychiatric illnesses;
- limited life expectancy;
- impaired liver or renal function;
- transitional cell carcinoma of the urethral margin or other surgical margins.

Relative contraindications specific for an orthotopic neobladder are high-dose pre-operative RT, complex urethral stricture disease, and severe urethral sphincter-related incontinence [321].

7.4.4.2 Patient selection for orthotopic diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports complications of RC, while ignoring the fact that most complications are diversion related [322]. Age alone is not a criterion for offering continent diversion [321, 323]. Comorbidity, cardiac and pulmonary function, and cognitive function, are all important factors that should be considered, along with the patient's social support and preference.

Age > 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended. However, there is no exact age for a strict contraindication. In most large series from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% in men and 50% in women [324-327]. Nevertheless, no RCTs comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

Recently, a retrospective study including 1,383 patients showed that the risk of a decline in estimated glomerular filtration rate (eGFR) did not significantly differ after ileal conduit vs. neobladder in patients with pre-operative chronic kidney disease 2 (eGFR 60-89 mL/min/1.73 m²) or 3a (eGFR 45-59 mL/min/1.73 m²) [328]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

7.4.4.2.1 Ureterocutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, stay at intensive care and length of hospital stay are lower in patients treated with

ureterocutaneostomy as compared to ileal conduit [329]. Therefore, in older, or otherwise compromised, patients who need a supravescical diversion, ureterocutaneostomy is the preferred procedure [330, 331]. Quality of life, which was assessed using the Bladder Cancer Index, showed equal urinary bother and function for patients treated with ileal conduit and ureterocutaneostomy [329].

However, others have demonstrated that, in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible [244]. Technically, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (transureteroureterocutaneostomy) or both ureters are directly anastomosed to the skin. Due to the smaller diameter of the ureters, stoma stenosis has been observed more often than in intestinal stomas [330].

In a retrospective multicentre study peri-operative morbidity was evaluated for urinary diversion using bowel as compared to ureterocutaneostomy. Patients selected for a ureterocutaneostomy were older and had a higher ASA score, while their mean Charlson score was lower (4.2 vs. 5.6, $p < 0.001$) [332].

Despite the limited comparative data available, it must be taken into consideration that older data and clinical experience suggest ureter stenosis at the skin level and ascending UTI are more frequent complications in ureterocutaneostomy compared to an ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [333].

7.4.4.2.2 Ileal conduit

The ileal conduit is still an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, ureteroileal leakage and stenosis [333]. The main complications in long-term follow-up studies are stomal complications in up to 24% of cases and functional and/or morphological changes of the UUT in up to 30% [334-336]. An increase in complications was seen with longer follow-up in the Berne series of 131 patients who were followed for a minimum of five years (median follow-up 98 months) [337]; the rate of complications increased from 45% at five years to 94% in those surviving > 15 years. In the latter group, 50% of patients developed UUT changes and 38% developed urolithiasis.

7.4.4.2.3 Continent cutaneous urinary diversion

A low-pressure detubularised ileal reservoir can be used as a continent cutaneous urinary diversion for self-catheterisation; gastric, ileocecal and sigma pouches have also been described [338-340]. Different anti-reflux techniques can be used [341]. Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% [342]. In a retrospective study of > 800 patients, stomal stenosis was seen in 23.5% of patients with an appendix stoma and 15% of those with an efferent intussuscepted ileal nipple [342]. Stone formation in the pouch occurred in 10% of patients [341-343]. In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in 8/44 patients (18%) [344].

7.4.4.2.4 Ureterocolonic diversion

The oldest and most common form of ureterocolonic diversion was primarily a refluxive and later an anti-refluxive connection of ureters to the intact rectosigmoid colon (uretero-rectosigmoidostomy) [345, 346]. Most indications for this procedure have become obsolete due to a high incidence of upper UTIs and the long-term risk of developing colon cancer [313, 314]. Bowel frequency and urge incontinence are additional adverse effects of this type of urinary diversion. However, it may be possible to circumvent the above-mentioned problems by interposing a segment of ileum between the ureters and rectum or sigmoid in order to augment capacity and avoid direct contact between the urothelium and colonic mucosa, as well as faeces and urine [347].

7.4.4.2.5 Orthotopic neobladder

An orthotopic bladder substitution to the urethra is now commonly used both in men and women. Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy [189, 243, 321]. In elderly patients (> 80 years), however, it is rarely performed, even in high-volume expert centres [348, 349]. The terminal ileum is the gastrointestinal segment most often used for bladder substitution. There is less experience with the ascending colon, including the caecum, and the sigmoid [243]. Emptying of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis, and sphincter relaxation. Early and late morbidity in up to 22% of the patients is reported [350, 351]. In two studies with 1,054 and 1,300 patients [321, 352], long-term complications included diurnal (8-10%) and nocturnal (20-30%) incontinence, ureterointestinal stenosis (3-18%), metabolic disorders, and vitamin B12 deficiency. In a recent study that compared cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit, there was no

difference in CSS between the two groups when adjusting for pathological stage [353]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [321, 354]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether neobladder is better for QoL compared to non-continent urinary diversion [355-357].

Various forms of UUT reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described [341, 351]. According to the long-term results, the UUT is protected sufficiently by either method.

In conclusion, standard RC in male patients with bladder neoplasms includes removal of the entire bladder, prostate, seminal vesicles, distal ureters (segment length undefined), and corresponding LNs (extent undefined) (LE: 2b). In female patients, standard RC includes removal of the entire bladder, urethra and adjacent vagina, uterus, distal ureters, and corresponding LNs.

A detailed investigation of the bladder neck prior to RC is important for women who are scheduled for an orthotopic bladder substitute [358]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12-16% [359]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Additionally, the tumours were at higher risk of advanced stage and nodal involvement [360].

Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions prefer ileal orthotopic neobladders and ileal conduits, based on clinical experience [361, 362]. In selected patients, such as patients with a single kidney, ureterocutaneostomy is surgically the least burdensome type of diversion (LE: 3). Recommendations related to RC and urinary diversions are listed in section 7.5.

7.4.5 **Morbidity and mortality**

In three long-term studies, and one population-based cohort study, the peri-operative mortality was reported as 1.2-3.2% at 30 days and 2.3-8.0% at 90 days [189, 322, 324, 363, 364]. In a large single-centre series, early complications (within three months of surgery) were seen in 58% of patients [322]. Late morbidity was usually linked to the type of urinary diversion (see also above) [325, 365]. Early morbidity associated with RC for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours [366]. In general, lower morbidity and (peri-operative) mortality have been observed by surgeons and in hospitals with a higher case load and therefore more experience [363, 367-371].

Table 7.6: Management of neobladder morbidity (30-64%) [372].

CLAVIEN System		Morbidity	Management
Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	Immediate complications:	
		Post-operative ileus	Nasogastric intubation (usually removed at J1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Post-operative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics (ATB), no ureteral catheter removal Check the 3 drainages (ureters and neobladder)
		Ureteral catheter obstruction	Inject 5cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase diuresis
		intra-abdominal urine leakage (anastomosis leakage)	Check drainages and watchful waiting
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non compressive lymphocele	Watchful waiting
		Mucus cork	Cough Indwelling catheter to remove the obstruction
		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
		Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Pulmonary embolism	Heparinotherapy ³		
Pyelonephritis	ATB and check kidney drainage (nephrostomy if necessary)		
Confusion or neurological disorder	Neuroleptics and avoid opioids		
Grade III	Requiring surgical, endoscopic or radiological intervention	Ureteral catheter accidentally dislodged	Indwelling leader to raise the ureteral catheter
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
		Ureteral reflux	No treatment if asymptomatic
III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage or intra-operative marsupialisation (cf grade III)
III-b	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy, as soon as possible
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)

Grade IV	Life-threatening complication (including central nervous system complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring intensive care/intensive care unit management.	Rectal necrosis	Colostomy
		Neobladder rupture	Nephrostomy and indwelling catheter/surgery for repairing neobladder
		Severe sepsis	ATB and check all the urinary drainages and computed tomography scan in emergency
IV-a	Single organ dysfunction (including dialysis)	Non-obstructive renal failure	Bicarbonate/aetiology treatment
IV-b	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Nephrostomy and ATB
Grade V	Death of a patient		
Suffix 'd'	If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.		

¹ A recent SR showed that peri-operative blood transfusion (PBT) in patients who undergo RC correlates with increased all-cause mortality, cancer specific mortality and cancer recurrence. The authors hypothesised that this may be caused by the suggested immunosuppressive effect of PBT. The foreign antigens in transfused blood induce immune suppression, which may lead to tumour cell spread, tumour growth and reduced survival in already immunosuppressed cancer patients. As other possible causes for this finding increased post-operative infections and blood incompatibility were mentioned [373].

² Intraoperative tranexamin acid infusion reduces peri-operative blood transfusion rates from 57.7% to 31.1%. There was no increase seen in peri-operative venous thromboembolism [374].

³ Hammond and co-workers reviewed 20,762 cases of venous thromboembolism (VTE) after major surgery and found cystectomy patients to have the second highest rate of VTE among all cancers studied [375]. These patients benefit from 30 days low-molecular-weight heparin prophylaxis. Subsequently, it was demonstrated that BMI > 30 and non-urothelial BCs are independently associated with VTE after cystectomy. In these patients extended (90 days) heparin prophylaxis should be considered [376].

7.4.6 Survival

According to a multi-institutional database of 888 consecutive patients undergoing RC for BC, the five-year recurrence-free survival was 58% and the CSS was 66% [377]. Recent external validation of post-operative nomograms for BC-specific mortality showed similar results, with bladder-CSS of 62% [378].

Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at five years and 60% and 43%, at ten years, respectively [176]. However, the five-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34-43% [175, 176, 379]. In a surgery-only study, the five-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [176].

A trend analysis according to the five-year survival and mortality rates of BC in the U.S.A., between 1973 and 2009 with a total of 148,315 BC patients, revealed an increased stage-specific five-year survival rate for all stages, except for metastatic disease [380].

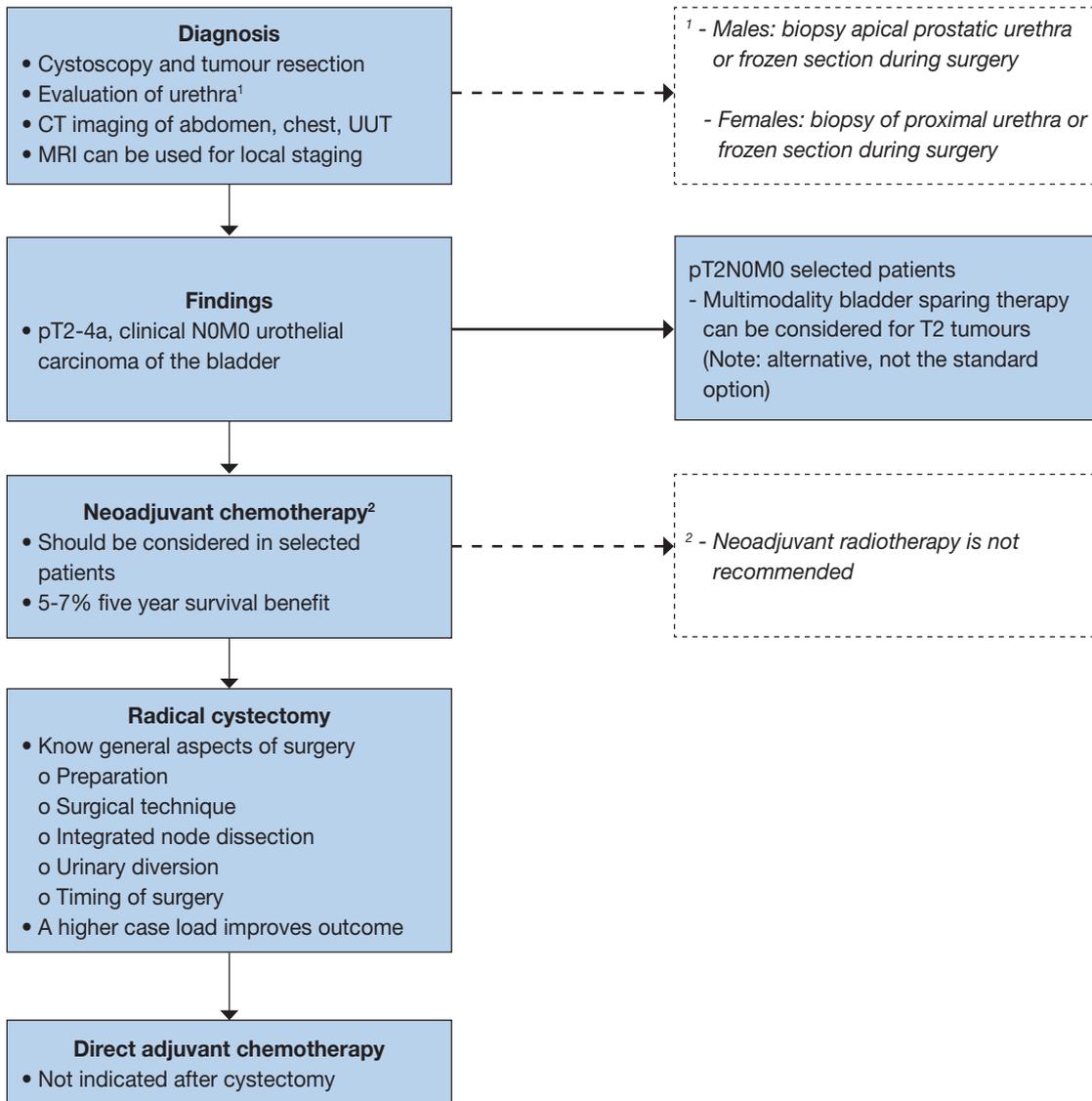
7.4.7 **Summary of evidence and recommendations for radical cystectomy and urinary diversion**

Summary of evidence	LE
For muscle-invasive bladder cancer, offer radical cystectomy as the curative treatment of choice.	3
A higher case load reduces morbidity and mortality of cystectomy.	3
Radical cystectomy includes removal of regional lymph nodes.	3
There are data to support that extended lymph node dissection (LND) (vs. standard or limited LND) improves survival after radical cystectomy.	3
Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as the outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
Laparoscopic cystectomy and robotic-assisted laparoscopic cystectomy are feasible but still investigational. Current best practice is open radical cystectomy.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted, graded system for cystectomy is the Clavien grading system.	2
No conclusive evidence exists as to the optimal extent of LND.	2a

Recommendations	GR
Do not delay cystectomy for > 3 months as it increases the risk of progression and cancer-specific mortality.	B
Before cystectomy, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	B
Offer an orthotopic bladder substitute or ileal conduit diversion to male and female patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection.	B
Do not offer pre-operative radiotherapy when subsequent cystectomy with urinary diversion is planned.	A
Pre-operative bowel preparation is not mandatory. "Fast track" measurements may reduce the time of bowel recovery.	C
Offer radical cystectomy in T2-T4a, N0M0, and high-risk non-MIBC (as outlined above).	A*
Perform a lymph node dissection as an integral part of cystectomy.	A
Preserve the urethra if margins are negative.	B
Check the urethra regularly if no bladder substitution is attached.	B

*Upgraded following EAU Working Panel consensus.

7.1: Flow chart for the management of T2-T4a N0M0 urothelial bladder cancer



CT = computed tomography; MRI = magnetic resonance imaging; UUT = upper urinary tract.

7.5 Unresectable tumours

7.5.1 Palliative cystectomy for muscle-invasive bladder carcinoma

Locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT. Palliative cystectomy with urinary diversion carries the greatest morbidity and should be considered for symptom relief only if there are no other options [381-383].

Locally advanced MIBC can be associated with ureteral obstruction due to a combination of mechanical blockage by the tumour and invasion of ureteral orifices by tumour cells. In a series of 61 patients with obstructive uraemia, RC was not an option in 23 patients, and obstruction was relieved using permanent nephrostomy tubes [384]. Another ten patients underwent palliative cystectomy, but local pelvic recurrence occurred in all ten patients within the first year of follow-up. Another small study (n = 20) showed that primary cystectomy for T4 BC was technically feasible and associated with a very tolerable therapy-related morbidity and mortality [385].

7.5.1.1 *Recommendations for unresectable tumours*

Recommendations	GR
Offer radical cystectomy as a palliative treatment to patients with inoperable locally advanced tumours (T4b).	B
Offer palliative cystectomy in patients with symptoms.	B

7.5.2 **Supportive care**7.5.2.1 *Obstruction of the UUT*

Unilateral (best kidney) or bilateral nephrostomy tubes provide the easiest solution for UUT obstruction, but patients find the tubes inconvenient and prefer ureteral stenting. However, stenting can be difficult to achieve, stents must be regularly replaced and there is the risk of stent obstruction or displacement. Another possible solution is a urinary diversion with, or without, a palliative cystectomy.

7.5.2.2 *Bleeding and pain*

In the case of bleeding, the patient must be screened first for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1-2% alum can be effective [386]. It can usually be done without any anaesthesia. The instillation of formalin (2.5-4% for 30 minutes) is a more aggressive and painful procedure, requiring anaesthesia. Formalin instillation has a higher risk of side-effects, e.g. bladder fibrosis, but is more likely to control the bleeding [386]. Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy for control of bleeding, and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73% [387]. Irritative bladder and bowel complaints due to irradiation are possible, but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90% [386]. Radical surgery is a last resort and includes cystectomy and diversion (see above Section 7.5.1).

7.6 **Bladder-sparing treatments for localised disease**7.6.1 ***Transurethral resection of bladder tumour (TURB)***

Transurethral resection of bladder tumour alone in patients with muscle-invasive bladder tumours is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumour [388]. In general, about half will still have to undergo RC for recurrent muscle-invasive cancer with a disease-specific mortality rate of up to 47% within this group [389]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [390, 391]. A prospective study by Solsona *et al.*, which included 133 patients with radical TURB and re-staging negative biopsies, reported a fifteen-year follow-up [391]. Thirty per cent had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After five, ten and fifteen years the results showed a CSS of 81.9%, 79.5%, and 76.7%, respectively and PFS rates with an intact bladder of 75.5%, 64.9%, and 57.8%, respectively.

In conclusion, TURB alone should only be considered as a therapeutic option for muscle-invasive disease after radical TURB, when the patient is unfit for cystectomy or a multimodality bladder-preserving approach, or refuses open surgery [392].

7.6.1.1 *Recommendation for transurethral resection of bladder tumour*

Recommendation	LE	GR
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	2a	B

7.6.2 ***External beam radiotherapy (EBRT)***

Current RT techniques with soft-tissue matching result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target dose for curative RT in BC is 60-66 Gy, with a subsequent boost using external RT or interstitial RT. The use of modern standard RT techniques results in major, related, late morbidity of the urinary bladder or bowel in less than 5% of tumour-free patients [393]. Acute diarrhoea is even more reduced with intensity-modulated RT [394]. Important prognostic factors for outcome include response to

RT, tumour size, hydronephrosis and completeness of the initial TURB. Additional prognostic factors reported were age and stage [395].

In 2007 long-term results were reported by Chung *et al.* [396]. A total of 340 patients with MIBC were treated with EBRT alone, EBRT with concurrent chemotherapy, or NAC followed by EBRT. The overall CR was 55% and the ten-year DSS and OS were 35% and 19%, respectively. Complete response was 64% after EBRT alone, 79% after concurrent chemotherapy (n = 36), and 52% after NAC (n = 57). Younger age, lower tumour stage and absence of CIS were associated with a significant improvement in survival.

A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [397], although this was not the case in a 2014 retrospective review using a propensity score analysis [398].

In conclusion, EBRT can be an alternative treatment in patients unfit for radical surgery.

7.6.2.1 Summary of evidence and recommendation for external beam radiotherapy

Summary of evidence	LE
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.	3

Recommendation	GR
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	B

7.6.3 Chemotherapy

Chemotherapy alone rarely produces durable complete remissions. In general, a clinical CR rate of up to 56%, as reported in some series, which must be weighed against a staging error of > 60% [399, 400]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival [199], though it may be confounded by patient selection.

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [197, 226, 401, 402]. Neoadjuvant chemotherapy with 2-3 cycles of MVAC or CMV has led to a downstaging of the primary tumour in different prospective series [197, 226, 401]. Pathological complete responses of primary bladder tumours were reached in 12-50% of patients after MVAC and in 12-22% of patients after gemcitabine/cisplatin (GC) in phase II and phase III trials [197, 226, 401, 403-410].

Contemporary series with GC followed by RC reported inferior pT0 rates, which may have been related to a lack of dose density and inappropriate delay of surgery [230].

For highly selected patients, a bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy, preferably with MVAC, may allow long-term survival with intact bladder [199]. However, this approach cannot be recommended for routine use.

7.6.3.1 Summary of evidence and recommendation for chemotherapy for muscle-invasive bladder tumours

Summary of evidence	LE
With cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients, complete and partial local responses have been reported.	2b

Recommendation	GR
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	A

7.6.4 Multimodality bladder-preserving treatment

Multimodality treatment (MMT) or trimodality treatment combines TURB, chemotherapy and radiation. The rationale for performing TURB and radiation is to achieve local tumour control. The addition of systemic chemotherapy or other radiosensitisers (mentioned below) aims at the potentiation of RT. Micrometastases

are targeted by platinum-based combination chemotherapy and this topic is covered in the section on NAC (see Section 7.2). The aim of multimodality therapy is to preserve the bladder and QoL, without compromising outcome. A collaborative review addressed this approach [411].

There are no completed RCTs to compare the outcome of MMT with the gold standard, RC, but this approach has been shown to be superior to RT alone [412, 413]. Many of the reported series have differing characteristics as compared to the large surgical series which typically have median ages in the mid-late 60s compared to mid-70s for some large RT series (reviewed in [412]). In the case of MMT, two distinct patterns of care may be distinguished: treatment aimed at patients fit for cystectomy and treatment aimed at older, less fit patients. For the former category MMT presents selective bladder preservation. In that case, the initial step is a radical TURB, where as much tumour as possible should be resected. This implies that proper patient selection (T2 tumours, no CIS) is critical [414]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, though extensive CIS and poor bladder function should both be regarded as strong contraindications.

Following TURB and staging, treatment comprises EBRT with concurrent radiosensitising drugs. Two schedules are in common use worldwide: a split dose format with interim cystoscopy is used in North America [414] whilst single-phase treatment is more commonly used elsewhere [412]. For radiosensitising chemotherapy, cisplatin [415] or mitomycin C plus 5-fluorouracil (5-FU) can be used [412], but also other schedules have been used. In particular, hypoxic cell sensitisation with nicotinamide and carbogen has been evaluated in a large phase III trial [416]. In a recent phase I trial gemcitabine was used [417]. The regimen was well tolerated with promising results.

With MMT, five-year CSS and OS rates are achieved from 50-82% and from 36-74% respectively [393, 412, 415, 416, 418-420]. Salvage cystectomy rates are 10-30% [412, 415, 420]. There are data that major complication rates are similar for salvage and primary cystectomy [421]. The majority of recurrences post-MMT are non invasive and can be managed conservatively [412]. The collaborative review comes to the conclusion that there are accumulating data suggesting that bladder preservation with MMT leads to acceptable outcomes and therefore may be considered a reasonable treatment option in well-selected patients as compared to RC [422]. It should also be considered in all patients where surgery is contraindicated, either relatively or absolutely as the factors that determine fitness for surgery and chemoradiotherapy differ.

A bladder-preserving multimodality strategy requires very close multidisciplinary co-operation and a high level of patient compliance. Even if a patient has shown a CR to a multimodality bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-term bladder monitoring is essential and patients should be counselled that this will be required. A recent subanalysis from two RTOG trials looked at CR (T0) and near CR (Ta or Tis) after MMT [423]. After a median follow up of 5.9 years 41/119 (35%) of these patients experienced a bladder recurrence, and fourteen required a salvage cystectomy. There was no difference between complete and near-complete responders.

7.6.4.1 Summary of evidence and recommendations for multimodality treatment in muscle-invasive bladder cancer

Summary of evidence	LE
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	2b

Recommendations	GR
Offer surgical intervention or multimodality treatments as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	B
Offer multimodality treatment as an alternative in selected, well-informed and compliant patients, especially for whom cystectomy is not an option.	B

7.7 Adjuvant chemotherapy

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate [421, 424] and is still infrequently used [193].

The general benefits of adjuvant chemotherapy include:

- chemotherapy is administered after accurate pathological staging, therefore treatment in patients at low risk for micrometastases is avoided;
- no delay in definitive surgical treatment.

The drawbacks of adjuvant chemotherapy are:

- assessment of *in vivo* chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem;
- delay or intolerance of chemotherapy, due to post-operative morbidity [425].

There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy [424, 426-431]. Individual patient data from six randomised trials [420, 432-435] of adjuvant chemotherapy were included in one meta-analysis [426] with 491 patients for survival analysis (unpublished data from Otto *et al.*, were included in the analysis). All these trials were suboptimal with serious deficiencies, including small sample size (underpowered), early cessation of patient entry, and flaws in design and statistical analysis, including irrelevant endpoints or a lack of recommendations concerning salvage chemotherapy for relapse or metastases [424]. In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [436], and one trial used cisplatin monotherapy [434]. These data were not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

In a 2014 meta-analysis [427], an additional three studies were included [428-430]. However, only 945 patients were included in this meta-analysis of nine trials, and none of the trials were fully accrued and no individual patient data were used [427]. For one trial, only an abstract was available at the time of the meta-analysis [429], and none of the included trials by themselves were significantly positive for OS in favour of adjuvant chemotherapy. In two of the trials, more modern chemotherapy regimens were used (gemcitabine/ cisplatin and paclitaxel/gemcitabine and cisplatin) [428, 429]. The HR for OS was 0.77 and there was a trend towards an OS benefit when including all nine trials. The effect was stronger for DFS (HR: 0.66; 95% CI: 0.48-0.92) and when stratified for the ratio of nodal positivity (HR: 0.64; 95% CI: 0.45- 0.91). The background of this finding was heterogeneity in outcomes observed between the included studies. After stratification of the studies by the ratio of node positivity, no further heterogeneity was identified. The HR for DFS associated with adjuvant cisplatin-based chemotherapy in studies with higher nodal involvement was 0.39 (95% CI: 0.28-0.54), compared with 0.89 (95% CI: 0.69-1.15) in studies with less nodal involvement.

Furthermore, a retrospective cohort analysis that included 3,974 patients after cystectomy and LND showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) [HR: 0.75; CI: 0.62-0.90] [437]. The most recent publication of the so far largest RCT (EORTC 30994), although not fully accrued, showed a significant improvement of PFS for immediate compared with deferred treatment (HR: 0.54; 95% CI: 0.4-0.73, $p < 0.0001$), there was, however, no significant OS benefit [438].

From the currently available evidence, it is still unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior, or if the two approaches are equivalent with respect to the endpoint of OS. Cisplatin-based combination chemotherapy results in long-term DFS, even in metastatic disease, mainly in patients with LN metastases only, and with a good PS [407, 439, 440]. In the most recent meta-analysis, the positive role of adjuvant chemotherapy for BC has been strengthened, however, still with a poor level of evidence [427]. Patients should be informed about potential chemotherapy options before RC, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

7.7.1 Recommendation for adjuvant chemotherapy

Recommendation	GR
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	B

7.8 Metastatic disease

7.8.1 Introduction

Half of the patients with muscle-invasive UC relapse after RC, depending on the pathological stage of the primary tumour and the nodal status. Local recurrence accounts for 30% of relapses, whereas distant metastases are more common. Ten to fifteen percent of patients are already metastatic at diagnosis [441]. Before the development of effective chemotherapy, patients with metastatic UC rarely had a median survival that exceeded three-six months [442].

7.8.1.1 Prognostic factors and treatment decisions

Prognostic factors are crucial for assessing phase II study results and stratifying phase III trials [405, 409].

In a multivariate analysis, Karnofsky PS of $\leq 80\%$ and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC [409]. They have also been validated for newer combination chemotherapy regimens [443-445].

For patients refractory to, or progressing shortly after, platinum-based combination chemotherapy, four prognostic groups have been established, based on three adverse factors that have been developed in patients treated with vinflunine and that have been validated in an independent data set: Hb < 10 g/dL; presence of liver metastases; and ECOG PS ≥ 1 [446]. Cisplatin, has also been administered in patients with a GFR as low as 40 mL/min., using different schedules. The respective studies were mostly small size phase I and II trials [447-450]. In one phase III trial the cut off for cisplatin eligibility was ≥ 50 mL/min [451].

7.8.1.2 *Comorbidity in metastatic disease*

Comorbidity is defined as “the presence of one or more disease(s) in addition to an index disease” (see Section 6.2.1). Comorbidity increases with age. However, chronological age does not necessarily correlate with functional impairment. Different evaluation systems are being used to screen patients as potentially fit or unfit for chemotherapy, but age alone should not be used to base treatment selection on [452].

7.8.1.3 *Not eligible for cisplatin (unfit)*

The EORTC conducted the first randomised phase II/III trial for urothelial carcinoma patients who were unfit for cisplatin chemotherapy [453]. The EORTC definitions were GFR < 60 mL/min and/or PS 2.

An international survey among BC experts [454] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria has to be present: PS > 1 ; GFR ≤ 60 mL/min; grade ≥ 2 audiometric loss; peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure [455].

More than 50% of patients with UC are not eligible for cisplatin-based chemotherapy [456-459].

Renal function assessment in UC is of utmost importance for treatment selection. Calculation of creatinine clearance (CrCl) (24-h urine collection) with current formulae tend to underestimate clearance in patients aged > 65 years compared to measured CrCl [456, 460].

7.8.2 *Single-agent chemotherapy*

Response rates to single-agent, first-line chemotherapy vary. The most robust data have shown a response rate of about 25% for first- and second-line gemcitabine in several phase II trials [461, 462]. Responses with single agents are usually short-lived, complete responses are rare and no long-term DFS has been reported. The median survival in such patients is only six-nine months.

7.8.3 *Standard first-line chemotherapy for fit patients*

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s (for a review see [463]). Methotrexate, vinblastine, adriamycin plus cisplatin MVAC and GC prolonged survival to up to 14.8 and 13.8 months, respectively, compared to monotherapy and older combinations. Neither of the two combinations is superior to the other, but equivalence has not been tested. Response rates were 46% and 49% for MVAC and GC, respectively. The long-term survival results have confirmed the anticipated equivalence of the two regimens [439]. The major difference between the above-mentioned combinations is toxicity. The lower toxicity of GC [158] has resulted in it becoming a new standard regimen [464]. Methotrexate, vinblastine, adriamycin plus cisplatin is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) [464, 465].

High-dose intensity MVAC (HD-MVAC) combined with G-CSF is less toxic and more efficacious than standard MVAC in terms of dose density, complete response, and two-year survival rate. However, there is no significant difference in median survival between the two regimens [466, 467]. In general, all disease sites have been shown to respond to cisplatin-based combination chemotherapy. A response rate of 66% and 77% with MVAC and HD-MVAC, respectively, has been reported in retroperitoneal LNs vs. 29% and 33% at extranodal sites [466]. The disease sites also have an impact on long-term survival. In lymph-node-only disease, 20.9% of patients were alive at five years compared to only 6.8% of patients with visceral metastases [439].

Further intensification of treatment using the new paclitaxel, cisplatin and gemcitabine (PCG) triple regimen did not result in a significant improvement in OS in the intent-to-treat (ITT) population of a large randomised phase III trial, comparing PCG triple regimen to GC [468]. However, the overall response rate (ORR) was higher with the triple regimen (56% vs. 44%; $p = 0.0031$), and the trend for OS improvement in the ITT population (15.8 vs. 12.7 months; HR = 0.85, $p = 0.075$) became significant in the eligible population. Adding paclitaxel to GC did not induce major additional side effects. Grade 4 neutropenia was more common (35.8% vs. 20% for GC), as

was febrile neutropenia (13.2% vs. 4.3%), and the need for G-CSF was higher (17% vs. 11%). Gemcitabine/cisplatin alone caused more G4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%). Paclitaxel, cisplatin and gemcitabine is an additional option for first-line treatment of UC.

7.8.4 **Carboplatin-containing chemotherapy for fit patients**

Carboplatin-containing chemotherapy is not equivalent to cisplatin combinations, and should not be considered interchangeable or standard. Several randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy have produced lower CR rates and shorter OS for the carboplatin arms [469].

7.8.5 **Non-platinum combination chemotherapy**

Different combinations of gemcitabine and paclitaxel have been studied as first- and second-line treatments. Apart from severe pulmonary toxicity with a weekly schedule of both drugs, this combination is well tolerated and produces response rates between 38% and 60% in both lines. Non-platinum combination chemotherapy has not been compared to standard cisplatin chemotherapy in randomised trials, therefore, it is not recommended for first-line use in cisplatin-eligible patients [470-477].

7.8.6 **Chemotherapy in patients unfit for cisplatin**

Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [455]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GemCarbo) in patients unfit for cisplatin. Both regimens were active. Severe acute toxicity (SAT) was 13.6% in patients treated with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI. Further analysis showed that in patients with PS 2 and impaired renal function, combination chemotherapy provided limited benefit [453]. The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group [453]. Phase III data have confirmed these results [445].

7.8.7 **Second-line treatment**

Second-line chemotherapy data are highly variable and prognostic factors have been established recently (see Section 7.8.1.1) [446]. A reasonable strategy may be to re-challenge former cisplatin-sensitive patients if progression occurs at least six to twelve months after first-line cisplatin-based combination chemotherapy. Second-line response rates of paclitaxel (weekly), docetaxel, nab-paclitaxel [478] oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [462, 479, 480]. Although gemcitabine has also shown excellent response rates in second-line use, most patients already receive this drug as part of their front-line treatment [461].

Paclitaxel/gemcitabine studies have shown response rates of 38-60%. No randomised phase III trial with an adequate comparator arm has been conducted to assess the true value and OS benefit of this second-line combination [442, 476, 481].

Vinflunine, a novel third-generation vinca alkaloid, provided promising results in phase II trials [482]. A randomised phase III trial compared vinflunine plus best supportive care (BSC) against BSC alone in patients progressing after first-line treatment with platinum-containing combination chemotherapy for metastatic disease [483]. The results showed a modest ORR (8.6%), a clinical benefit with a favourable safety profile and, most importantly, a survival benefit in favour of vinflunine, which was statistically significant in the eligible patient population (not in the ITT population). For second-line treatment of advanced or metastatic UC, this trial reached the highest level of evidence ever reported. Currently, in Europe, vinflunine is the only approved second-line treatment. Vinflunine has not been approved for this indication in the United States.

7.8.8 **Low-volume disease and post-chemotherapy surgery**

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with LN but no other metastases, good PS, and adequate renal function, including a high number of CRs, with up to 20% of patients achieving long-term DFS [439, 467, 484, 485]. The role of surgery after chemotherapy is still unclear. Although some studies suggest a survival benefit and QoL improvement, the level of evidence supporting this practice is very limited [486-500]. A retrospective study of post-chemotherapy surgery after a partial or complete response has indicated that surgery may contribute to long-term DFS in selected patients [410, 501, 502].

7.8.9 **Treatment of bone metastases**

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30-40% [503]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [504]. Bisphosphonates reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption. In a small pilot study in patients with BC, SREs caused by bone metastases were delayed [505]. Denosumab is a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor- κ B ligand), thereby inhibiting osteoclast function and preventing generalised bone resorption and local bone destruction. Denosumab is not inferior to zoledronic acid (ZA) in preventing or delaying SREs in patients with advanced MBD, including patients with UC [506]. Denosumab has recently been approved by the European Medicines Agency (EMA) for treatment of patients with bone metastases from solid tumours. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [504].

Patients treated with ZA or denosumab should be informed about possible side effects and receive prophylactic treatment for jaw osteonecrosis and hypocalcaemia, which is more common with denosumab. Aggressive calcium and vitamin D supplementation is recommended. Dosing regimens of ZA should follow regulatory recommendations and should be adjusted according to pre-existing medical conditions [507]. For denosumab, no dose adjustments are required for variations in renal function.

7.8.10 **Role of immunotherapy**

Immunomodulatory therapies using checkpoint inhibition, particularly with antibodies directed against the programmed cell death-1 (PD-1) protein or its ligand (PD-L1) have been tested. Atezolizumab, the first PD-L1 inhibitor was approved by the US Food and Drug Administration (FDA) in May 2016 for patients that have progressed during or after previous platinum-based chemotherapy. In a phase-II two-cohort study including 310 patients, the objective response rate was 15% independent of the expression of PD-L1. Progression-free survival was 2.1 and OS was 7.9 months. According to the expression level of PD-L1 numbers for response rate, PFS and OS were greater for patients with high expression but responses occurred also in patients with no expression of PD-L1. The toxicity profile of atezolizumab was favourable. Results of the phase III trial (NCT02302807) comparing atezolizumab with second-line chemotherapy are pending [508, 509].

7.8.11 **Summary of evidence and recommendations for metastatic disease**

Summary of evidence	LE
In a first-line setting, performance status (PS) and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS \geq 1 and low haemoglobin (< 10 g/dL)	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term disease-free survival reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
Non-platinum combination chemotherapy produces substantial responses in first- and second-line settings.	2a
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
There is no defined standard chemotherapy for unfit patients with advanced or metastatic urothelial cancer (UC).	2b
Vinflunine reaches the highest level of evidence ever reported for second-line use.	1b
Post-chemotherapy surgery after partial or complete response may contribute to long-term disease-free survival in selected patients.	3
Zoledronic acid and denosumab have been approved for all cancer types including UC, because they reduce and delay skeletal related events in metastatic bone disease.	1b
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase-II trial.	2a

Recommendations	GR
First-line treatment for fit patients:	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	A
Do not use carboplatin and non-platinum combination chemotherapy.	B
First-line treatment in patients ineligible (unfit) for cisplatin:	
Use carboplatin combination chemotherapy or single agents.	C
For cisplatin-ineligible (unfit) patients, with performance status 2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, offer carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin.	B
Second-line treatment:	
Offer vinflunine to patients progressing after platinum-based combination chemotherapy for metastatic disease. Alternatively, offer treatment within a clinical trial setting.	A*
Offer zoledronic acid or denosumab to treat bone metastases.	B

* Grade A recommendation is weakened since the key studies did not reach statistical significance.

GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PCG = paclitaxel, cisplatin, gemcitabine.

7.8.12 Biomarkers

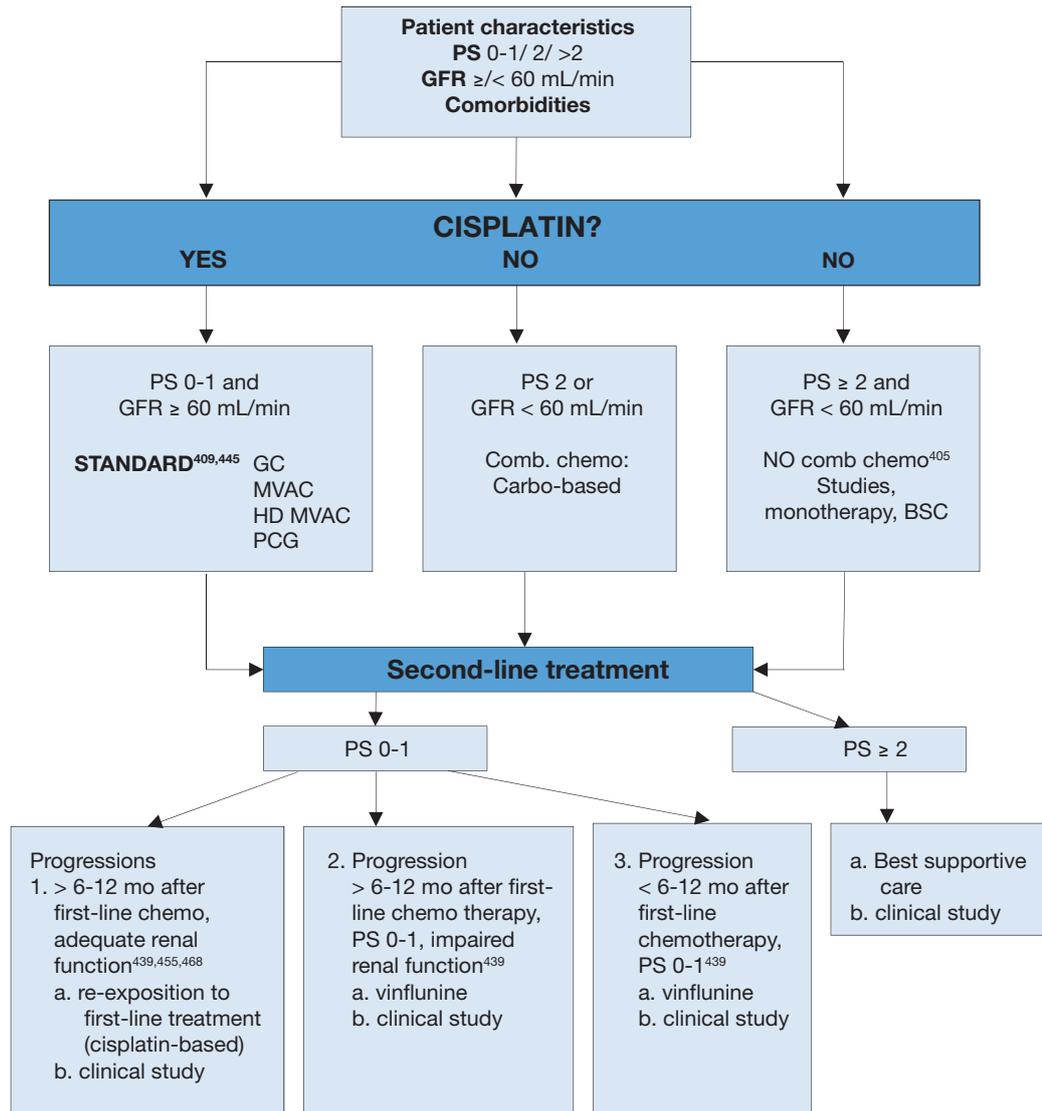
Modest disease control rates, with sporadic marked responses, in some patients with UC have led to the investigation of biomarkers for assessment of post-operative prognosis and the potential value of peri-operative chemotherapy, and as predictors of response to chemotherapy or its monitoring. Most of the biomarkers are associated with tumour angiogenesis. Small studies, usually retrospective, have investigated microvessel density, altered p53 tumour expression [510], serum vascular endothelial growth factor [511], urinary and tissue basic fibroblast growth factor [512], urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 [513], and more recently, thrombospondin-1 [514], circulating tumour cells [515, 516], and multidrug resistance gene expression [517]. Although a few biomarkers have shown potential, as yet, there is insufficient evidence to support their routine clinical use (LE: 3).

7.8.12.1 Recommendation for the use of biomarkers

Recommendation	GR
Do not use biomarkers in daily clinical practice since they have no impact on predicting outcome, treatment decisions, or monitoring therapy in muscle-invasive bladder cancer.	A*

*Upgraded following panel consensus.

Figure 7.2: Flow chart for the management of metastatic urothelial cancer



BSC = best supportive care; GC = gemcitabine plus cisplatin; GFR = glomerular filtration rate; MVAC = methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS = performance status; PCG = paclitaxel, cisplatin, gemcitabine.

7.9 Quality of life

7.9.1 Introduction

The evaluation of HRQoL considers physical, psychological, emotional and social functioning.

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT (Functional Assessment of Cancer Therapy)-G [518], EORTC QLQ-C30 [519], EORTC QLQ-BLM (muscle-invasive BC module) [520], and SF (Short Form)-36 [521, 522] and recently the BCI questionnaire specifically designed and validated for BC patients [523].

A psychometric test, such as the FACT-BL, should be used for recording BC morbidity. New intensive interviewing techniques have added valuable information to our knowledge of HRQoL, which greatly depends on patients' individual preferences [524].

7.9.2 Choice of urinary diversion

There is controversy about which type of urinary diversion is best for a patient's HRQoL [243]. Most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit [525]. Another study reported that, although urinary function is better in conduit patients, at long-term follow up (> 1 year) the urinary bother is the same in both diversion groups .

A SR based on 18 studies showed a slight, but not significant, better QoL in patients with an orthotopic diversion [526]. However, analysing only the studies comparing exclusively ileal conduit vs. ileal orthotopic neobladder, the advantage in QoL of the latter group was significant.

Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes [362, 520, 527]. Patients with an orthotopic substitution had significantly better physical function and a more active lifestyle compared to patients with an ileal conduit. It is important to note that HRQoL parameters are independent prognostic factors for OS [528]. Patients with a continent bladder-substitute generally scored more favourably than those with an incontinent diversion, as judged by body image, social activity and physical function [527, 529]. Note that all studies investigated mostly male patients. Also of interest is the urinary bother in female neobladder. Bartsch and co-workers found in 56 female patients day-time and night-time incontinence rates of respectively 29.6% and 35.2%. Thirty-five patients (62.5%) performed clean intermittent catheterisation, which is much worse compared to male neobladder patients. Moreover, patients with non-organ-confined disease ($p = 0.04$) and patients with a college degree ($p = 0.001$) showed worse outcome on HRQoL scores [530].

Nevertheless, the HRQoL outcome is most likely a result of good patient selection. An older more isolated patient is probably better served with an ileal conduit whereas a younger patient with more interest in body image and sexuality is better off with an orthotopic diversion.

7.9.3 *Non-curative or metastatic bladder cancer*

In non-curative or metastatic BC, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life [531]. There is limited literature describing HRQoL in BC patients receiving palliative care [532], but there are reports of bladder-related symptoms relieved by palliative surgery [385], RT [533], and/or chemotherapy [534].

Alternative definitive treatments of MIBC, e.g. trimodality bladder-sparing procedures, have shown similar survival times compared to cystectomy. However, the impact on HRQoL has been controversial [136, 393, 535-538].

7.9.4 *Summary of evidence and recommendations for health-related quality of life*

Summary of evidence	LE
No randomised, prospective health-related quality of life (HRQoL) study has evaluated the different forms of definitive treatment for MIBC.	2b
In most patient groups studied, the overall HRQoL after cystectomy remains good, irrespective of the type of urinary diversion used. The suggestion that continent diversions are associated with a better HRQoL has not been sufficiently substantiated.	
Important determinants of (subjective) quality of life are a patient's personality, coping style and social support.	

Recommendations	GR
Use validated questionnaires to assess HRQoL in patients with MIBC.	B
Offer a continent urinary diversion unless a patient's comorbidities, tumour variables and coping abilities present clear contraindications.	C
Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.	C
Encourage patients to actively participate in the decision-making process.	
Provide clear and exhaustive information on all potential benefits and side-effects, allowing patients to make informed decisions.	A

8. FOLLOW-UP

8.1 Introduction

An appropriate schedule for disease monitoring should be based on:

- natural timing of recurrence;
- probability and site of recurrence;
- functional monitoring after urinary diversion;
- possible treatment of recurrence [539].

Nomograms on CSS following RC have been developed and externally validated. However, their wider use cannot be recommended until further data becomes available [540, 541].

Surveillance protocols are commonly based on patterns of recurrence observed from retrospective series. Diagnosis of asymptomatic recurrence based on routine oncological follow-up and results from retrospective studies are controversial [542, 543]. Importantly, these retrospective studies use different follow-up regimens and imaging techniques that make final analysis and conclusive recommendations difficult. Prospective trials demonstrating the effectiveness of follow up after RC and its impact on OS are lacking [544].

8.2 Site of recurrence

8.2.1 Local recurrence

Local recurrence takes place in soft tissues at the original surgical site or LNs in the area of LND. Lymph node involvement above the aortic bifurcation can be considered metastatic recurrence [542].

Contemporary cystectomy has a 5-15% probability of pelvic recurrence. Most recurrence manifests during the first 24 months, often within six to eighteen months after surgery. However, late recurrence can occur up to five years after cystectomy. Pathological stage and LN status are predictive for pelvic recurrence, as well as positive margins, extent of LND, and peri-operative chemotherapy [545].

Patients have poor prognosis after pelvic recurrence. Even with treatment, the median survival ranges from four to eight months following diagnosis. Definitive therapy can prolong survival, but mostly provides significant palliation of symptoms. Treatment comprises systemic chemotherapy, local surgery, or RT [544].

8.2.2 Distant recurrence

Distant recurrence is seen in up to 50% of patients treated with cystectomy. Stage and nodal involvement are risk factors [546]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with LN involvement (range 52-70%) [547].

The most likely sites for distant recurrence are LNs, lungs, liver and bone. Nearly 90% of distant recurrence appears within the first three years after RC, mainly in the first two years, although late recurrence has been described after > 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9-26 months [548-550].

Despite periodic monitoring, > 50% of metastases are diagnosed after symptom appearance.

The value of monitoring in diagnosis of asymptomatic metastases and its impact on survival is questionable. Some studies have demonstrated no impact on survival despite using routine monitoring, although others have suggested that diagnosis of asymptomatic metastases, especially in the lungs, improves survival [542, 543]. Consideration must also be given to the possibility of longer survival in patients with minimal metastatic disease undergoing multimodal treatment, including metastasectomy. There are reports of survival rates of 28-33% at five years in patients undergoing resection of metastases after objective response to chemotherapy [495, 502].

The incidence of new urethral tumours after RC is 1.5-6.0% in men, with a mean recurrence-free interval of 13.5-39.0 months and median survival of 28-38 months, of which > 50% die from systemic disease.

Secondary urethral tumours are likely to occur at one to three years after surgery. Prophylactic urethrectomy at cystectomy is no longer justified in most patients. Independent predictors for urethral recurrence are: cystectomy for NMIBC, prostate involvement, and history of recurrent NMIBC [544].

In women, the main risk factor is bladder neck disease. Many studies have demonstrated that the risk of urethral recurrence after orthotopic diversion (0.9-4.0%) [551-554] is significantly less than after non-orthotopic diversion (6.4-11.1%) [545, 551, 553].

There is limited data and agreement about urethral follow-up, with some recommending routine surveillance with urethral wash and urine cytology [554], and others doubting the need for routine urethral surveillance [552, 555, 556]. Urethral washes and urine cytology do not appear to affect survival [555, 557]. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptotically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [544].

Treatment is influenced by local stage and grade of urethral occurrence:

- in urethral CIS, BCG instillations have success rates of 83% [554];
- in invasive disease, urethrectomy should be performed if the urethra is the only site of disease;
- in distant disease, systemic chemotherapy is indicated [558].

Upper urinary urothelial carcinomas occur in 1.8-6.0% of cases and represent the most common sites of late recurrence (three years DFS following RC). Median OS is 10-55 months, and 60-67% of patients die of metastatic disease [544].

A meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigation, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used in surveillance, the rate of primary detection was 7% and 29.6% with UUT imaging [559]. This meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Radical nephroureterectomy can prolong survival [560].

8.2.3 Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	LE	Recommendation	GR
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	2b	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	C
Distant recurrence	Poor prognosis.	2b	Offer chemotherapy as the first option, and consider metastasectomy in case of unique metastasis site.	C
Upper urinary tract recurrence	Multifocal disease (non-muscle-invasive bladder cancer/carcinoma <i>in situ</i> or positive ureteral margins).		See EAU guidelines on Upper Urinary Tract Urothelial Carcinomas.	
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	3	Use local conservative treatment for non-invasive tumour.	C
			Offer urethrectomy in isolated invasive disease.	B
			Do not use urethral washes and cytology.	A

Although general recommendations are not advised based on high level of evidence, closer follow-up could be considered in patients with locally advanced disease or LN involvement. The suggested follow-up includes four-monthly CT scans during the first year, six-monthly until the third year, and annual imaging thereafter.

Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC which can develop late (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used to assess the UUT [559].

8.3 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients having undergone a urinary diversion deserve functional follow up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow up.

This rate increases over time, and exceeds 54% after fifteen years of follow up. Therefore, long-term follow up of functional outcomes is desirable [544] (LE: 3), and may stop after fifteen years.

The functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of

renal function, urinary infections, urolithiasis, stenosis of uretero-intestinal anastomosis, stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction [544]. Especially in women, approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [530]. Recently a 21% increased risk of fractures was described as compared to no cystectomy, due to chronic metabolic acidosis and subsequent long-term bone loss [561].

9. REFERENCES

1. Rouprêt, M., *et al.* Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma. EAU Guidelines 2017. Edn presented at the 32nd EAU Annual Congress London 2017.
2. Babjuk, M., *et al.* Guidelines on Non-muscle-invasive bladder cancer (TaT1 and CIS). 2017. Edn presented at the 32nd EAU Annual Congress London 2017.
3. Gakis, G., *et al.* Guidelines on Primary Urethral Carcinoma EAU Guidelines 2017. Edn presented at the 32nd EAU Annual Congress London 2017.
4. Witjes, A.J., *et al.* Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. *Eur Urol*, 2017. 71: 462.
<https://www.ncbi.nlm.nih.gov/pubmed/27375033>
5. Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
6. Ferlay, J., *et al.* Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*, 2013. 49: 1374.
<https://www.ncbi.nlm.nih.gov/pubmed/23485231>
7. GLOBOCAN 2012 v1.0: Estimated cancer incidence, mortality and prevalence worldwide in 2012. 2016.
<http://globocan.iarc.fr/Default.aspx>
8. Burger, M., *et al.* Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*, 2013. 63: 234.
<https://www.ncbi.nlm.nih.gov/pubmed/22877502>
9. Bosetti, C., *et al.* Trends in mortality from urologic cancers in Europe, 1970-2008. *Eur Urol*, 2011. 60: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/21497988>
10. Chavan, S., *et al.* International variations in bladder cancer incidence and mortality. *Eur Urol*, 2014. 66: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/24451595>
11. Comperat, E., *et al.* Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. *Virchows Arch*, 2015. 466: 589.
<https://www.ncbi.nlm.nih.gov/pubmed/25697540>
12. Steinmaus, C., *et al.* Increased lung and bladder cancer incidence in adults after in utero and early-life arsenic exposure. *Cancer Epidemiol Biomarkers Prev*, 2014. 23: 1529.
<https://www.ncbi.nlm.nih.gov/pubmed/24859871>
13. Freedman, N.D., *et al.* Association between smoking and risk of bladder cancer among men and women. *JAMA*, 2011. 306: 737.
<https://www.ncbi.nlm.nih.gov/pubmed/21846855>
14. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum, 2004. 83: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/15285078>
15. Brennan, P., *et al.* Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer*, 2000. 86: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/10738259>
16. Gandini, S., *et al.* Tobacco smoking and cancer: a meta-analysis. *Int J Cancer*, 2008. 122: 155.
<https://www.ncbi.nlm.nih.gov/pubmed/17893872>
17. Pashos, C.L., *et al.* Bladder cancer: epidemiology, diagnosis, and management. *Cancer Pract*, 2002. 10: 311.
<https://www.ncbi.nlm.nih.gov/pubmed/12406054>
18. Harling, M., *et al.* Bladder cancer among hairdressers: a meta-analysis. *Occup Environ Med*, 2010. 67: 351.
<https://www.ncbi.nlm.nih.gov/pubmed/20447989>

19. Weistenhofer, W., *et al.* N-acetyltransferase-2 and medical history in bladder cancer cases with a suspected occupational disease (BK 1301) in Germany. *J Toxicol Environ Health A*, 2008. 71: 906.
<https://www.ncbi.nlm.nih.gov/pubmed/18569594>
20. Rushton, L., *et al.* Occupation and cancer in Britain. *Br J Cancer*, 2010. 102: 1428.
<https://www.ncbi.nlm.nih.gov/pubmed/20424618>
21. Chrouser, K., *et al.* Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol*, 2005. 174: 107.
<https://www.ncbi.nlm.nih.gov/pubmed/15947588>
22. Nieder, A.M., *et al.* Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: a population based cohort study. *J Urol*, 2008. 180: 2005.
<https://www.ncbi.nlm.nih.gov/pubmed/18801517>
23. Zelefsky, M.J., *et al.* Incidence of secondary cancer development after high-dose intensity-modulated radiotherapy and image-guided brachytherapy for the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys*, 2012. 83: 953.
<https://www.ncbi.nlm.nih.gov/pubmed/22172904>
24. Zamora-Ros, R., *et al.* Flavonoid and lignan intake in relation to bladder cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Br J Cancer*, 2014.
<https://www.ncbi.nlm.nih.gov/pubmed/25121955>
25. Schistosomes, liver flukes and *Helicobacter pylori*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum*, 1994. 61: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/7715068>
26. Gouda, I., *et al.* Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. *J Egypt Natl Canc Inst*, 2007. 19: 158.
<https://www.ncbi.nlm.nih.gov/pubmed/19034337>
27. Salem, H.K., *et al.* Changing patterns (age, incidence, and pathologic types) of schistosoma-associated bladder cancer in Egypt in the past decade. *Urology*, 2012. 79: 379.
<https://www.ncbi.nlm.nih.gov/pubmed/22112287>
28. Pelucchi, C., *et al.* Mechanisms of disease: The epidemiology of bladder cancer. *Nat Clin Pract Urol*, 2006. 3: 327.
<https://www.ncbi.nlm.nih.gov/pubmed/16763645>
29. Liu, S., *et al.* The impact of female gender on bladder cancer-specific death risk after radical cystectomy: a meta-analysis of 27,912 patients. *Int Urol Nephrol*, 2015. 47: 951.
<https://www.ncbi.nlm.nih.gov/pubmed/25894962>
30. Waldhoer, T., *et al.* Sex Differences of \geq pT1 Bladder Cancer Survival in Austria: A Descriptive, Long-Term, Nation-Wide Analysis Based on 27,773 Patients. *Urol Int*, 2015. 94: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/25833466>
31. Patafio, F.M., *et al.* Is there a gender effect in bladder cancer? A population-based study of practice and outcomes. *Can Urol Assoc J*, 2015. 9: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/26316913>
32. Cohn, J.A., *et al.* Sex disparities in diagnosis of bladder cancer after initial presentation with hematuria: a nationwide claims-based investigation. *Cancer*, 2014. 120: 555.
<https://www.ncbi.nlm.nih.gov/pubmed/24496869>
33. Dietrich, K., *et al.* Parity, early menopause and the incidence of bladder cancer in women: a case-control study and meta-analysis. *Eur J Cancer*, 2011. 47: 592.
<https://www.ncbi.nlm.nih.gov/pubmed/21067913>
34. Scosyrev, E., *et al.* Sex and racial differences in bladder cancer presentation and mortality in the US. *Cancer*, 2009. 115: 68.
<https://www.ncbi.nlm.nih.gov/pubmed/19072984>
35. Stenzl, A. Words of wisdom. Re: sex and racial differences in bladder cancer presentation and mortality in the US. *Eur Urol*, 2010. 57: 729.
<https://www.ncbi.nlm.nih.gov/pubmed/20965044>
36. Murta-Nascimento, C., *et al.* Risk of bladder cancer associated with family history of cancer: do low-penetrance polymorphisms account for the increase in risk? *Cancer Epidemiol Biomarkers Prev*, 2007. 16: 1595.
<https://www.ncbi.nlm.nih.gov/pubmed/17684133>
37. Figueroa, J.D., *et al.* Genome-wide association study identifies multiple loci associated with bladder cancer risk. *Hum Mol Genet*, 2014. 23: 1387.
<https://www.ncbi.nlm.nih.gov/pubmed/24163127>

38. Rothman, N., *et al.* A multi-stage genome-wide association study of bladder cancer identifies multiple susceptibility loci. *Nat Genet*, 2010. 42: 978.
<https://www.ncbi.nlm.nih.gov/pubmed/20972438>
39. Kiemeny, L.A., *et al.* Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. *Nat Genet*, 2008. 40: 1307.
<https://www.ncbi.nlm.nih.gov/pubmed/18794855>
40. Stenzl, A. Current concepts for urinary diversion in women. *Eur Urol (EAU Update series 1)*, 2003: 91. [No abstract available].
41. Varinot, J., *et al.* Full analysis of the prostatic urethra at the time of radical cystoprostatectomy for bladder cancer: impact on final disease stage. *Virchows Arch*, 2009. 455: 449.
<https://www.ncbi.nlm.nih.gov/pubmed/19841937>
42. Hansel, D.E., *et al.* A contemporary update on pathology standards for bladder cancer: transurethral resection and radical cystectomy specimens. *Eur Urol*, 2013. 63: 321.
<https://www.ncbi.nlm.nih.gov/pubmed/23088996>
43. Herr, H.W. Pathologic evaluation of radical cystectomy specimens. *Cancer*, 2002. 95: 668.
<https://www.ncbi.nlm.nih.gov/pubmed/12209761>
44. Fajkovic, H., *et al.* Extranodal extension is a powerful prognostic factor in bladder cancer patients with lymph node metastasis. *Eur Urol*, 2013. 64: 837.
<https://www.ncbi.nlm.nih.gov/pubmed/22877503>
45. Fritsche, H.M., *et al.* Prognostic value of perinodal lymphovascular invasion following radical cystectomy for lymph node-positive urothelial carcinoma. *Eur Urol*, 2013. 63: 739.
<https://www.ncbi.nlm.nih.gov/pubmed/23079053>
46. Ku, J.H., *et al.* Lymph node density as a prognostic variable in node-positive bladder cancer: a meta-analysis. *BMC Cancer*, 2015. 15: 447.
<https://www.ncbi.nlm.nih.gov/pubmed/26027955>
47. Neuzillet, Y., *et al.* Positive surgical margins and their locations in specimens are adverse prognosis features after radical cystectomy in non-metastatic carcinoma invading bladder muscle: results from a nationwide case-control study. *BJU Int*, 2013. 111: 1253.
<https://www.ncbi.nlm.nih.gov/pubmed/23331375>
48. Baltaci, S., *et al.* Reliability of frozen section examination of obturator lymph nodes and impact on lymph node dissection borders during radical cystectomy: results of a prospective multicentre study by the Turkish Society of Urooncology. *BJU Int*, 2011. 107: 547.
<https://www.ncbi.nlm.nih.gov/pubmed/20633004>
49. Jimenez, R.E., *et al.* Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression-free survival. *Am J Surg Pathol*, 2000. 24: 980.
<https://www.ncbi.nlm.nih.gov/pubmed/10895820>
50. Sjobahl, G., *et al.* A molecular taxonomy for urothelial carcinoma. *Clin Cancer Res*, 2012. 18: 3377.
<https://www.ncbi.nlm.nih.gov/pubmed/22553347>
51. Choi, W., *et al.* Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. *Cancer Cell*, 2014. 25: 152.
<https://www.ncbi.nlm.nih.gov/pubmed/24525232>
52. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th ed. 2016, Lyon, France
<http://publications.iarc.fr/Book-And-Report-Series/Who-Iarc-Classification-Of-Tumours/Who-Classification-Of-Tumours-Of-The-Urinary-System-And-Male-Genital-Organs-2016>
53. Sauter G, *et al.*, Tumours of the urinary system: non-invasive urothelial neoplasias., in WHO classification of classification of tumors of the urinary system and male genital organs. 2004, IARC Press: Lyon.
54. Kapur, P., *et al.* Primary adenocarcinoma of the urinary bladder: value of cell cycle biomarkers. *Am J Clin Pathol*, 2011. 135: 822.
<https://www.ncbi.nlm.nih.gov/pubmed/21571954>
55. Ploeg, M., *et al.* Clinical epidemiology of nonurothelial bladder cancer: analysis of the Netherlands Cancer Registry. *J Urol*, 2010. 183: 915.
<https://www.ncbi.nlm.nih.gov/pubmed/20083267>
56. Beltran, A.L., *et al.* Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder. *Virchows Arch*, 2014. 465: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/24878757>
57. Mukesh, M., *et al.* Small cell carcinoma of the urinary bladder: a 15-year retrospective review of treatment and survival in the Anglian Cancer Network. *BJU Int*, 2009. 103: 747.
<https://www.ncbi.nlm.nih.gov/pubmed/19076139>

58. Brierley JD., *et al.*, TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. 2017, Oxford.
<http://www.uicc.org/resources/tnm/publications-resources>
59. Jensen, J.B., *et al.* Incidence of occult lymph-node metastasis missed by standard pathological examination in patients with bladder cancer undergoing radical cystectomy. *Scand J Urol Nephrol*, 2011. 45: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/21767245>
60. Leissner, J., *et al.* Prognostic significance of vascular and perineural invasion in urothelial bladder cancer treated with radical cystectomy. *J Urol*, 2003. 169: 955.
<https://www.ncbi.nlm.nih.gov/pubmed/12576821>
61. Fossa, S.D., *et al.* Clinical significance of the “palpable mass” in patients with muscle-infiltrating bladder cancer undergoing cystectomy after pre-operative radiotherapy. *Br J Urol*, 1991. 67: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/8653315>
62. Wijkstrom, H., *et al.* Evaluation of clinical staging before cystectomy in transitional cell bladder carcinoma: a long-term follow-up of 276 consecutive patients. *Br J Urol*, 1998. 81: 686.
<https://www.ncbi.nlm.nih.gov/pubmed/9634042>
63. Ploeg, M., *et al.* Discrepancy between clinical staging through bimanual palpation and pathological staging after cystectomy. *Urol Oncol*, 2012. 30: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/20451418>
64. Lokeshwar, V.B., *et al.* Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. *Urology*, 2005. 66: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/16399415>
65. Raitanen, M.P., *et al.* Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. *Eur Urol*, 2002. 41: 284.
<https://www.ncbi.nlm.nih.gov/pubmed/12180229>
66. van Rhijn, B.W., *et al.* Urine markers for bladder cancer surveillance: a systematic review. *Eur Urol*, 2005. 47: 736.
<https://www.ncbi.nlm.nih.gov/pubmed/15925067>
67. Barkan, G.A., *et al.* The Paris System for Reporting Urinary Cytology: The Quest to Develop a Standardized Terminology. *Adv Anat Pathol*, 2016. 23: 193.
<https://www.ncbi.nlm.nih.gov/pubmed/27233050>
68. Stenzl, A., *et al.* Hexaminolevulinic acid guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. *J Urol*, 2010. 184: 1907.
<https://www.ncbi.nlm.nih.gov/pubmed/20850152>
69. Burger, M., *et al.* Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinic acid cystoscopy: a meta-analysis of detection and recurrence based on raw data. *Eur Urol*, 2013. 64: 846.
<https://www.ncbi.nlm.nih.gov/pubmed/23602406>
70. Matzkin, H., *et al.* Transitional cell carcinoma of the prostate. *J Urol*, 1991. 146: 1207.
<https://www.ncbi.nlm.nih.gov/pubmed/1942262>
71. Mungan, M.U., *et al.* Risk factors for mucosal prostatic urethral involvement in superficial transitional cell carcinoma of the bladder. *Eur Urol*, 2005. 48: 760.
<https://www.ncbi.nlm.nih.gov/pubmed/16005563>
72. Kassouf, W., *et al.* Prostatic urethral biopsy has limited usefulness in counseling patients regarding final urethral margin status during orthotopic neobladder reconstruction. *J Urol*, 2008. 180: 164.
<https://www.ncbi.nlm.nih.gov/pubmed/18485384>
73. Walsh, D.L., *et al.* Dilemmas in the treatment of urothelial cancers of the prostate. *Urol Oncol*, 2009. 27: 352.
<https://www.ncbi.nlm.nih.gov/pubmed/18439852>
74. Lebet, T., *et al.* Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatocystectomy. *Eur Urol*, 1998. 33: 170.
<https://www.ncbi.nlm.nih.gov/pubmed/9519359>
75. Miladi, M., *et al.* The value of a second transurethral resection in evaluating patients with bladder tumours. *Eur Urol*, 2003. 43: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/12600426>
76. Jakse, G., *et al.* A second-look TUR in T1 transitional cell carcinoma: why? *Eur Urol*, 2004. 45: 539.
<https://www.ncbi.nlm.nih.gov/pubmed/15082193>

77. Brauers, A., *et al.* Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? *J Urol*, 2001. 165: 808.
<https://www.ncbi.nlm.nih.gov/pubmed/11176474>
78. Schips, L., *et al.* Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology*, 2002. 59: 220.
<https://www.ncbi.nlm.nih.gov/pubmed/11834389>
79. Grimm, M.O., *et al.* Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol*, 2003. 170: 433.
<https://www.ncbi.nlm.nih.gov/pubmed/12853793>
80. Divrik, R.T., *et al.* The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. *J Urol*, 2006. 175: 1641.
<https://www.ncbi.nlm.nih.gov/pubmed/16600720>
81. Jahnsen, S., *et al.* Results of second-look resection after primary resection of T1 tumour of the urinary bladder. *Scand J Urol Nephrol*, 2005. 39: 206.
<https://www.ncbi.nlm.nih.gov/pubmed/16127800>
82. Damiano, R., *et al.* Clinicopathologic features of prostate adenocarcinoma incidentally discovered at the time of radical cystectomy: an evidence-based analysis. *Eur Urol*, 2007. 52: 648.
<https://www.ncbi.nlm.nih.gov/pubmed/17600614>
83. Gakis, G., *et al.* Incidental prostate cancer at radical cystoprostatectomy: implications for apex-sparing surgery. *BJU Int*, 2010. 105: 468.
<https://www.ncbi.nlm.nih.gov/pubmed/20102366>
84. Svatek, R.S., *et al.* Intravesical tumor involvement of the trigone is associated with nodal metastasis in patients undergoing radical cystectomy. *Urology*, 2014. 84: 1147.
<https://www.ncbi.nlm.nih.gov/pubmed/25174656>
85. Jewett, H.J. Proceedings: Cancer of the bladder. Diagnosis and staging. *Cancer*, 1973. 32: 1072.
<https://www.ncbi.nlm.nih.gov/pubmed/4757902>
86. Paik, M.L., *et al.* Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. *J Urol*, 2000. 163: 1693.
<https://www.ncbi.nlm.nih.gov/pubmed/10799162>
87. Barentsz, J.O., *et al.* Primary staging of urinary bladder carcinoma: the role of MRI and a comparison with CT. *Eur Radiol*, 1996. 6: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/8797968>
88. Barentsz, J.O., *et al.* Staging urinary bladder cancer after transurethral biopsy: value of fast dynamic contrast-enhanced MR imaging. *Radiology*, 1996. 201: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/8816542>
89. Mallampati, G.K., *et al.* MR imaging of the bladder. *Magn Reson Imaging Clin N Am*, 2004. 12: 545.
<https://www.ncbi.nlm.nih.gov/pubmed/15271370>
90. Rajesh, A., *et al.* Bladder cancer: evaluation of staging accuracy using dynamic MRI. *Clin Radiol*, 2011. 66: 1140.
<https://www.ncbi.nlm.nih.gov/pubmed/21924408>
91. Thomsen, H.S. Nephrogenic systemic fibrosis: history and epidemiology. *Radiol Clin North Am*, 2009. 47: 827.
<https://www.ncbi.nlm.nih.gov/pubmed/19744597>
92. Kundra, V., *et al.* Imaging in oncology from the University of Texas M. D. Anderson Cancer Center. Imaging in the diagnosis, staging, and follow-up of cancer of the urinary bladder. *AJR Am J Roentgenol*, 2003. 180: 1045.
<https://www.ncbi.nlm.nih.gov/pubmed/12646453>
93. Kim, B., *et al.* Bladder tumor staging: comparison of contrast-enhanced CT, T1- and T2-weighted MR imaging, dynamic gadolinium-enhanced imaging, and late gadolinium-enhanced imaging. *Radiology*, 1994. 193: 239.
<https://www.ncbi.nlm.nih.gov/pubmed/8090898>
94. Kim, J.K., *et al.* Bladder cancer: analysis of multi-detector row helical CT enhancement pattern and accuracy in tumor detection and perivesical staging. *Radiology*, 2004. 231: 725.
<https://www.ncbi.nlm.nih.gov/pubmed/15118111>
95. Jager, G.J., *et al.* Pelvic adenopathy in prostatic and urinary bladder carcinoma: MR imaging with a three-dimensional T1-weighted magnetization-prepared-rapid gradient-echo sequence. *AJR Am J Roentgenol*, 1996. 167: 1503.
<https://www.ncbi.nlm.nih.gov/pubmed/8956585>

96. Yang, W.T., *et al.* Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. *AJR Am J Roentgenol*, 2000. 175: 759.
<https://www.ncbi.nlm.nih.gov/pubmed/10954463>
97. Kim, S.H., *et al.* Uterine cervical carcinoma: evaluation of pelvic lymph node metastasis with MR imaging. *Radiology*, 1994. 190: 807.
<https://www.ncbi.nlm.nih.gov/pubmed/8115631>
98. Kim, S.H., *et al.* Uterine cervical carcinoma: comparison of CT and MR findings. *Radiology*, 1990. 175: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/2315503>
99. Oyen, R.H., *et al.* Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. *Radiology*, 1994. 190: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/8284375>
100. Barentsz, J.O., *et al.* MR imaging of the male pelvis. *Eur Radiol*, 1999. 9: 1722.
<https://www.ncbi.nlm.nih.gov/pubmed/10602944>
101. Dorfman, R.E., *et al.* Upper abdominal lymph nodes: criteria for normal size determined with CT. *Radiology*, 1991. 180: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/2068292>
102. Swinnen, G., *et al.* FDG-PET/CT for the preoperative lymph node staging of invasive bladder cancer. *Eur Urol*, 2010. 57: 641.
<https://www.ncbi.nlm.nih.gov/pubmed/19477579>
103. Kibel, A.S., *et al.* Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. *J Clin Oncol*, 2009. 27: 4314.
<https://www.ncbi.nlm.nih.gov/pubmed/19652070>
104. Lu, Y.Y., *et al.* Clinical value of FDG PET or PET/CT in urinary bladder cancer: a systemic review and meta-analysis. *Eur J Radiol*, 2012. 81: 2411.
<https://www.ncbi.nlm.nih.gov/pubmed/21899971>
105. Vargas, H.A., *et al.* Prospective evaluation of MRI, (1)(1)C-acetate PET/CT and contrast-enhanced CT for staging of bladder cancer. *Eur J Radiol*, 2012. 81: 4131.
<https://www.ncbi.nlm.nih.gov/pubmed/22858427>
106. Cowan, N.C. CT urography for hematuria. *Nat Rev Urol*, 2012. 9: 218.
<https://www.ncbi.nlm.nih.gov/pubmed/22410682>
107. Chow, L.C., *et al.* Split-bolus MDCT urography with synchronous nephrographic and excretory phase enhancement. *AJR Am J Roentgenol*, 2007. 189: 314.
<https://www.ncbi.nlm.nih.gov/pubmed/17646456>
108. Cowan, N.C., *et al.* Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. *BJU Int*, 2007. 99: 1363.
<https://www.ncbi.nlm.nih.gov/pubmed/17428251>
109. Fritz, G.A., *et al.* Multiphase multidetector-row CT (MDCT) in detection and staging of transitional cell carcinomas of the upper urinary tract. *Eur Radiol*, 2006. 16: 1244.
<https://www.ncbi.nlm.nih.gov/pubmed/16404565>
110. Maheshwari, E., *et al.* Split-bolus MDCT urography: Upper tract opacification and performance for upper tract tumors in patients with hematuria. *AJR Am J Roentgenol*, 2010. 194: 453.
<https://www.ncbi.nlm.nih.gov/pubmed/20093609>
111. Sudakoff, G.S., *et al.* Multidetector computerized tomography urography as the primary imaging modality for detecting urinary tract neoplasms in patients with asymptomatic hematuria. *J Urol*, 2008. 179: 862.
<https://www.ncbi.nlm.nih.gov/pubmed/18221955>
112. Wang, L.J., *et al.* Diagnostic accuracy of transitional cell carcinoma on multidetector computerized tomography urography in patients with gross hematuria. *J Urol*, 2009. 181: 524.
<https://www.ncbi.nlm.nih.gov/pubmed/19100576>
113. Wang, L.J., *et al.* Multidetector computerized tomography urography is more accurate than excretory urography for diagnosing transitional cell carcinoma of the upper urinary tract in adults with hematuria. *J Urol*, 2010. 183: 48.
<https://www.ncbi.nlm.nih.gov/pubmed/19913253>
114. Jinzaki, M., *et al.* Comparison of CT urography and excretory urography in the detection and localization of urothelial carcinoma of the upper urinary tract. *AJR Am J Roentgenol*, 2011. 196: 1102.
<https://www.ncbi.nlm.nih.gov/pubmed/21512076>

115. Van Der Molen, A.J., *et al.* CT urography: definition, indications and techniques. A guideline for clinical practice. *Eur Radiol*, 2008. 18: 4.
<https://www.ncbi.nlm.nih.gov/pubmed/17973110>
116. Albani, J.M., *et al.* The role of computerized tomographic urography in the initial evaluation of hematuria. *J Urol*, 2007. 177: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/17222650>
117. Gray Sears, C.L., *et al.* Prospective comparison of computerized tomography and excretory urography in the initial evaluation of asymptomatic microhematuria. *J Urol*, 2002. 168: 2457.
<https://www.ncbi.nlm.nih.gov/pubmed/12441939>
118. Girvin, F., *et al.* Pulmonary nodules: detection, assessment, and CAD. *AJR Am J Roentgenol*, 2008. 191: 1057.
<https://www.ncbi.nlm.nih.gov/pubmed/18806142>
119. Heidenreich, A., *et al.* Imaging studies in metastatic urogenital cancer patients undergoing systemic therapy: recommendations of a multidisciplinary consensus meeting of the Association of Urological Oncology of the German Cancer Society. *Urol Int*, 2010. 85: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/20693823>
120. Braendengen, M., *et al.* Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. *Br J Urol*, 1996. 77: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/8653315>
121. Brismar, J., *et al.* Bone scintigraphy in staging of bladder carcinoma. *Acta Radiol*, 1988. 29: 251.
<https://www.ncbi.nlm.nih.gov/pubmed/2965914>
122. Lauenstein, T.C., *et al.* Whole-body MR imaging: evaluation of patients for metastases. *Radiology*, 2004. 233: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/15317952>
123. Schmidt, G.P., *et al.* Whole-body MR imaging of bone marrow. *Eur J Radiol*, 2005. 55: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/15950099>
124. Yang, Z., *et al.* Is whole-body fluorine-18 fluorodeoxyglucose PET/CT plus additional pelvic images (oral hydration-voiding-refilling) useful for detecting recurrent bladder cancer? *Ann Nucl Med*, 2012. 26: 571.
<https://www.ncbi.nlm.nih.gov/pubmed/22763630>
125. Maurer, T., *et al.* Diagnostic efficacy of [11C]choline positron emission tomography/computed tomography compared with conventional computed tomography in lymph node staging of patients with bladder cancer prior to radical cystectomy. *Eur Urol*, 2012. 61: 1031.
<https://www.ncbi.nlm.nih.gov/pubmed/22196847>
126. Yoshida, S., *et al.* Role of diffusion-weighted magnetic resonance imaging in predicting sensitivity to chemoradiotherapy in muscle-invasive bladder cancer. *Int J Radiat Oncol Biol Phys*, 2012. 83: e21.
<https://www.ncbi.nlm.nih.gov/pubmed/22414281>
127. Game, X., *et al.* Radical cystectomy in patients older than 75 years: assessment of morbidity and mortality. *Eur Urol*, 2001. 39: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/11464032>
128. Clark, P.E., *et al.* Radical cystectomy in the elderly: comparison of clinical outcomes between younger and older patients. *Cancer*, 2005. 104: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/15912515>
129. May, M., *et al.* Results from three municipal hospitals regarding radical cystectomy on elderly patients. *Int Braz J Urol*, 2007. 33: 764.
<https://www.ncbi.nlm.nih.gov/pubmed/18199344>
130. Lawrentschuk, N., *et al.* Prevention and management of complications following radical cystectomy for bladder cancer. *Eur Urol*, 2010. 57: 983.
<https://www.ncbi.nlm.nih.gov/pubmed/20227172>
131. Donahue, T.F., *et al.* Risk factors for the development of parastomal hernia after radical cystectomy. *J Urol*, 2014. 191: 1708.
<https://www.ncbi.nlm.nih.gov/pubmed/24384155>
132. Djaladat, H., *et al.* The association of preoperative serum albumin level and American Society of Anesthesiologists (ASA) score on early complications and survival of patients undergoing radical cystectomy for urothelial bladder cancer. *BJU Int*, 2014. 113: 887.
<https://www.ncbi.nlm.nih.gov/pubmed/23906037>
133. Garg, T., *et al.* Preoperative serum albumin is associated with mortality and complications after radical cystectomy. *BJU Int*, 2014. 113: 918.
<https://www.ncbi.nlm.nih.gov/pubmed/24053616>

134. Rochon, P.A., *et al.* Comorbid illness is associated with survival and length of hospital stay in patients with chronic disability. A prospective comparison of three comorbidity indices. *Med Care*, 1996. 34: 1093.
<https://www.ncbi.nlm.nih.gov/pubmed/8911426>
135. Feinstein, A.R. The pre-therapeutic classification of co-morbidity in chronic disease. *J Chron Dis*, 1970. 23: 455.
<http://www.sciencedirect.com/science/article/pii/0021968170900548>
136. Zietman, A.L., *et al.* Organ-conserving approaches to muscle-invasive bladder cancer: future alternatives to radical cystectomy. *Ann Med*, 2000. 32: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/10711576>
137. Lughezzani, G., *et al.* A population-based competing-risks analysis of the survival of patients treated with radical cystectomy for bladder cancer. *Cancer*, 2011. 117: 103.
<https://www.ncbi.nlm.nih.gov/pubmed/20803606>
138. Froehner, M., *et al.* Complications following radical cystectomy for bladder cancer in the elderly. *Eur Urol*, 2009. 56: 443.
<https://www.ncbi.nlm.nih.gov/pubmed/19481861>
139. de Groot, V., *et al.* How to measure comorbidity. a critical review of available methods. *J Clin Epidemiol*, 2003. 56: 221.
<https://www.ncbi.nlm.nih.gov/pubmed/12725876>
140. Linn, B.S., *et al.* Cumulative illness rating scale. *J Am Geriatr Soc*, 1968. 16: 622.
<https://www.ncbi.nlm.nih.gov/pubmed/5646906>
141. Kaplan, M.H., *et al.* The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. *J Chronic Dis*, 1974. 27: 387.
<https://www.ncbi.nlm.nih.gov/pubmed/4436428>
142. Charlson, M.E., *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*, 1987. 40: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/3558716>
143. Greenfield, S., *et al.* The importance of co-existent disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement. *Comorbidity and outcomes after hip replacement. Med Care*, 1993. 31: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/8433577>
144. Paleri, V., *et al.* Applicability of the adult comorbidity evaluation - 27 and the Charlson indexes to assess comorbidity by notes extraction in a cohort of United Kingdom patients with head and neck cancer: a retrospective study. *J Laryngol Otol*, 2002. 116: 200.
<https://www.ncbi.nlm.nih.gov/pubmed/11893262>
145. Litwin, M.S., *et al.* Assessment of prognosis with the total illness burden index for prostate cancer: aiding clinicians in treatment choice. *Cancer*, 2007. 109: 1777.
<https://www.ncbi.nlm.nih.gov/pubmed/17354226>
146. Mayr, R., *et al.* Predictive capacity of four comorbidity indices estimating perioperative mortality after radical cystectomy for urothelial carcinoma of the bladder. *BJU Int*, 2012. 110: E222.
<https://www.ncbi.nlm.nih.gov/pubmed/22314129>
147. Morgan, T.M., *et al.* Predicting the probability of 90-day survival of elderly patients with bladder cancer treated with radical cystectomy. *J Urol*, 2011. 186: 829.
<https://www.ncbi.nlm.nih.gov/pubmed/21788035>
148. Abdollah, F., *et al.* Development and validation of a reference table for prediction of postoperative mortality rate in patients treated with radical cystectomy: a population-based study. *Ann Surg Oncol*, 2012. 19: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/21701925>
149. Miller, D.C., *et al.* The impact of co-morbid disease on cancer control and survival following radical cystectomy. *J Urol*, 2003. 169: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/12478114>
150. Koppie, T.M., *et al.* Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. *Cancer*, 2008. 112: 2384.
<https://www.ncbi.nlm.nih.gov/pubmed/18404699>
151. Bolenz, C., *et al.* Management of elderly patients with urothelial carcinoma of the bladder: guideline concordance and predictors of overall survival. *BJU Int*, 2010. 106: 1324.
<https://www.ncbi.nlm.nih.gov/pubmed/20500510>

152. Yoo, S., *et al.* Does radical cystectomy improve overall survival in octogenarians with muscle-invasive bladder cancer? *Korean J Urol*, 2011. 52: 446.
<https://www.ncbi.nlm.nih.gov/pubmed/21860763>
153. Mayr, R., *et al.* Comorbidity and performance indices as predictors of cancer-independent mortality but not of cancer-specific mortality after radical cystectomy for urothelial carcinoma of the bladder. *Eur Urol*, 2012. 62: 662.
<https://www.ncbi.nlm.nih.gov/pubmed/22534059>
154. Hall, W.H., *et al.* An electronic application for rapidly calculating Charlson comorbidity score. *BMC Cancer*, 2004. 4: 94.
<https://www.ncbi.nlm.nih.gov/pubmed/15610554>
155. Extermann, M., *et al.* Comorbidity and functional status are independent in older cancer patients. *J Clin Oncol*, 1998. 16: 1582.
<https://www.ncbi.nlm.nih.gov/pubmed/9552069>
156. Blagden, S.P., *et al.* Performance status score: do patients and their oncologists agree? *Br J Cancer*, 2003. 89: 1022.
<https://www.ncbi.nlm.nih.gov/pubmed/12966419>
157. Logothetis, C.J., *et al.* Escalated MVAC with or without recombinant human granulocyte-macrophage colony-stimulating factor for the initial treatment of advanced malignant urothelial tumors: results of a randomized trial. *J Clin Oncol*, 1995. 13: 2272.
<https://www.ncbi.nlm.nih.gov/pubmed/7666085>
158. von der Maase, H., *et al.* Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol*, 2000. 18: 3068.
<https://www.ncbi.nlm.nih.gov/pubmed/11001674>
159. Niegisch, G., *et al.* Prognostic factors in second-line treatment of urothelial cancers with gemcitabine and paclitaxel (German Association of Urological Oncology trial AB20/99). *Eur Urol*, 2011. 60: 1087.
<https://www.ncbi.nlm.nih.gov/pubmed/21839579>
160. Cohen, H.J., *et al.* A controlled trial of inpatient and outpatient geriatric evaluation and management. *N Engl J Med*, 2002. 346: 905.
<https://www.ncbi.nlm.nih.gov/pubmed/11907291>
161. Balducci, L., *et al.* General guidelines for the management of older patients with cancer. *Oncology (Williston Park)*, 2000. 14: 221.
<https://www.ncbi.nlm.nih.gov/pubmed/11195414>
162. Castagneto, B., *et al.* Single-agent gemcitabine in previously untreated elderly patients with advanced bladder carcinoma: response to treatment and correlation with the comprehensive geriatric assessment. *Oncology*, 2004. 67: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/15459492>
163. van Rhijn, B.W., *et al.* Molecular markers for urothelial bladder cancer prognosis: toward implementation in clinical practice. *Urol Oncol*, 2014. 32: 1078.
<https://www.ncbi.nlm.nih.gov/pubmed/25217465>
164. Amin, M.B., *et al.* Best practices recommendations in the application of immunohistochemistry in the bladder lesions: report from the International Society of Urologic Pathology consensus conference. *Am J Surg Pathol*, 2014. 38: e20.
<https://www.ncbi.nlm.nih.gov/pubmed/25029121>
165. Choi, W., *et al.* Intrinsic basal and luminal subtypes of muscle-invasive bladder cancer. *Nat Rev Urol*, 2014. 11: 400.
<https://www.ncbi.nlm.nih.gov/pubmed/24960601>
166. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*, 2014. 507: 315.
<http://www.nature.com/nature/journal/v507/n7492/full/nature12965.html>
167. Mitra, A.P., *et al.* Potential role for targeted therapy in muscle-invasive bladder cancer: lessons from the cancer genome atlas and beyond. *Urol Clin North Am*, 2015. 42: 201.
<https://www.ncbi.nlm.nih.gov/pubmed/25882562>
168. Sylvester, R.J., *et al.* Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol*, 2006. 49: 466.
<https://www.ncbi.nlm.nih.gov/pubmed/16442208>

169. Cambier, S., *et al.* EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. *Eur Urol*, 2015. <https://www.ncbi.nlm.nih.gov/pubmed/26210894>
170. Sylvester, R.J., *et al.* Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guerin, and bacillus Calmette-Guerin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. *Eur Urol*, 2010. 57: 766. <https://www.ncbi.nlm.nih.gov/pubmed/20034729>
171. Sylvester, R.J., *et al.* Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol*, 2002. 168: 1964. <https://www.ncbi.nlm.nih.gov/pubmed/12394686>
172. Bohle, A., *et al.* Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology*, 2004. 63: 682. <https://www.ncbi.nlm.nih.gov/pubmed/15072879>
173. Malmstrom, P.U., *et al.* An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. *Eur Urol*, 2009. 56: 247. <https://www.ncbi.nlm.nih.gov/pubmed/19409692>
174. Hautmann, R.E., *et al.* Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. *J Urol*, 2006. 176: 486. <https://www.ncbi.nlm.nih.gov/pubmed/16813874>
175. Madersbacher, S., *et al.* Radical cystectomy for bladder cancer today--a homogeneous series without neoadjuvant therapy. *J Clin Oncol*, 2003. 21: 690. <https://www.ncbi.nlm.nih.gov/pubmed/12586807>
176. Stein, J.P., *et al.* Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol*, 2001. 19: 666. <https://www.ncbi.nlm.nih.gov/pubmed/15912515>
177. Schwaibold, H.E., *et al.* The value of a second transurethral resection for T1 bladder cancer. *BJU Int*, 2006. 97: 1199. <https://www.ncbi.nlm.nih.gov/pubmed/16566814>
178. Dalbagni, G., *et al.* Clinical outcome in a contemporary series of restaged patients with clinical T1 bladder cancer. *Eur Urol*, 2009. 56: 903. <https://www.ncbi.nlm.nih.gov/pubmed/19632765>
179. van den Bosch, S., *et al.* Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. *Eur Urol*, 2011. 60: 493. <https://www.ncbi.nlm.nih.gov/pubmed/21664041>
180. Herr, H.W., *et al.* Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol*, 2001. 166: 1296. <https://www.ncbi.nlm.nih.gov/pubmed/11547061>
181. Kamat, A.M., *et al.* The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. *J Urol*, 2006. 175: 881. <https://www.ncbi.nlm.nih.gov/pubmed/16469571>
182. Palou, J., *et al.* Female gender and carcinoma *in situ* in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guerin. *Eur Urol*, 2012. 62: 118. <https://www.ncbi.nlm.nih.gov/pubmed/22101115>
183. Fernandez-Gomez, J., *et al.* Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. *J Urol*, 2009. 182: 2195. <https://www.ncbi.nlm.nih.gov/pubmed/19758621>
184. Pansadoro, V., *et al.* Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacille Calmette-Guerin: 18-year experience. *Urology*, 2002. 59: 227. <https://www.ncbi.nlm.nih.gov/pubmed/11834391>
185. Margel, D., *et al.* Long-term follow-up of patients with Stage T1 high-grade transitional cell carcinoma managed by Bacille Calmette-Guerin immunotherapy. *Urology*, 2007. 69: 78. <https://www.ncbi.nlm.nih.gov/pubmed/17270621>
186. Willis, D.L., *et al.* Clinical outcomes of cT1 micropapillary bladder cancer. *J Urol*, 2015. 193: 1129. <https://www.ncbi.nlm.nih.gov/pubmed/25254936>

187. Raj, G.V., *et al.* Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol*, 2007. 177: 1283.
<https://www.ncbi.nlm.nih.gov/pubmed/17382713>
188. Yates, D.R., *et al.* Treatment options available for bacillus Calmette-Guerin failure in non-muscle-invasive bladder cancer. *Eur Urol*, 2012. 62: 1088.
<https://www.ncbi.nlm.nih.gov/pubmed/22959049>
189. Stein, J.P., *et al.* Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. *World J Urol*, 2006. 24: 296.
<https://www.ncbi.nlm.nih.gov/pubmed/11157016>
190. Dalbagni, G., *et al.* Cystectomy for bladder cancer: a contemporary series. *J Urol*, 2001. 165: 1111.
<https://www.ncbi.nlm.nih.gov/pubmed/11257649>
191. Bassi, P., *et al.* Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol*, 1999. 161: 1494.
<https://www.ncbi.nlm.nih.gov/pubmed/10210380>
192. Ghoneim, M.A., *et al.* Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. *J Urol*, 1997. 158: 393.
<https://www.ncbi.nlm.nih.gov/pubmed/18485392>
193. David, K.A., *et al.* Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. *J Urol*, 2007. 178: 451.
<https://www.ncbi.nlm.nih.gov/pubmed/17561135>
194. Porter, M.P., *et al.* Patterns of use of systemic chemotherapy for Medicare beneficiaries with urothelial bladder cancer. *Urol Oncol*, 2011. 29: 252.
<https://www.ncbi.nlm.nih.gov/pubmed/19450992>
195. Sanchez-Ortiz, R.F., *et al.* An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol*, 2003. 169: 110.
<https://www.ncbi.nlm.nih.gov/pubmed/12478115>
196. Stein, J.P. Contemporary concepts of radical cystectomy and the treatment of bladder cancer. *J Urol*, 2003. 169: 116.
<https://www.ncbi.nlm.nih.gov/pubmed/12478116>
197. Grossman, H.B., *et al.* Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med*, 2003. 349: 859.
<https://www.ncbi.nlm.nih.gov/pubmed/12944571>
198. Sherif, A., *et al.* Neoadjuvant cisplatin based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. *Eur Urol*, 2004. 45: 297.
<https://www.ncbi.nlm.nih.gov/pubmed/12623505>
199. Sternberg, C.N., *et al.* Can patient selection for bladder preservation be based on response to chemotherapy? *Cancer*, 2003. 97: 1644.
<https://www.ncbi.nlm.nih.gov/pubmed/12655521>
200. Herr, H.W., *et al.* Surgery of invasive bladder cancer: is pathologic staging necessary? *Semin Oncol*, 1990. 17: 590.
<https://www.ncbi.nlm.nih.gov/pubmed/2218571>
201. Griffiths, G., *et al.* International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol*, 2011. 29: 2171.
<https://www.ncbi.nlm.nih.gov/pubmed/21502557>
202. Bassi P, *et al.* Neoadjuvant M-VAC chemotherapy of invasive bladder cancer: The G.U.O.N.E. multicenter phase III trial. *Eur Urol* 1998. Suppl 33: 142. [No abstract available].
203. Sherif, A., *et al.* Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer -- Nordic cystectomy trial 2. *Scand J Urol Nephrol*, 2002. 36: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/12623505>
204. Sengelov, L., *et al.* Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. *Acta Oncol*, 2002. 41: 447.
<https://www.ncbi.nlm.nih.gov/pubmed/12442921>
205. Italian Bladder Cancer Study Group (GISTV), Neoadjuvant treatment for locally advanced bladder cancer: a randomized prospective clinical trial. *J Chemother* 1996. 8: 345. [No abstract available].
206. Orsatti, M., *et al.* Alternating chemo-radiotherapy in bladder cancer: a conservative approach. *Int J Radiat Oncol Biol Phys*, 1995. 33: 173.
<https://www.ncbi.nlm.nih.gov/pubmed/7642415>

207. Marcuello, E., *et al.* 1155 A phase III trial of neoadjuvant chemotherapy (NCT) in patients (PTS) with invasive bladder cancer (IBC). Preliminary results: NCT improves pathological complete response rate. *Eur J Cancer*. 31: S241.
[http://www.ejancer.com/article/0959-8049\(95\)96401-X/abstract](http://www.ejancer.com/article/0959-8049(95)96401-X/abstract)
208. Shipley, W.U., *et al.* Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol*, 1998. 16: 3576.
<https://www.ncbi.nlm.nih.gov/pubmed/9817278>
209. Cannobio L. *et al.* A randomized study between neoadjuvant chemoradiotherapy (CT-RT) before radical cystectomy and cystectomy alone in bladder cancer. A 6 year follow-up. *Proc Am Soc Clin Oncol* 1995. 14: abstr 654. [No abstract available].
210. Abol-Enein H. *et al.* Neo-adjuvant chemotherapy in the treatment of invasive transitional bladder cancer. A controlled prospective randomized study. *Br J Urol* 1997. 79 174.
<https://www.researchgate.net/publication/279621730>
211. Abol-Enein, H. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. *Lancet*, 2003. 361: 1927.
<https://www.ncbi.nlm.nih.gov/pubmed/12801735>
212. Winquist, E., *et al.* Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. *J Urol*, 2004. 171: 561.
<https://www.ncbi.nlm.nih.gov/pubmed/14713760>
213. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol*, 2005. 48: 202.
<https://www.ncbi.nlm.nih.gov/pubmed/14713760>
214. Letocha, H., *et al.* Positron emission tomography with L-methyl-11C-methionine in the monitoring of therapy response in muscle-invasive transitional cell carcinoma of the urinary bladder. *Br J Urol*, 1994. 74: 767.
<https://www.ncbi.nlm.nih.gov/pubmed/7827849>
215. Nishimura, K., *et al.* The effects of neoadjuvant chemotherapy and chemo-radiation therapy on MRI staging in invasive bladder cancer: comparative study based on the pathological examination of whole layer bladder wall. *Int Urol Nephrol*, 2009. 41: 869.
<https://www.ncbi.nlm.nih.gov/pubmed/19396568>
216. Barentsz, J.O., *et al.* Evaluation of chemotherapy in advanced urinary bladder cancer with fast dynamic contrast-enhanced MR imaging. *Radiology*, 1998. 207: 791.
<https://www.ncbi.nlm.nih.gov/pubmed/9609906>
217. Krajewski, K.M., *et al.* Optimisation of the size variation threshold for imaging evaluation of response in patients with platinum-refractory advanced transitional cell carcinoma of the urothelium treated with vinflunine. *Eur J Cancer*, 2012. 48: 1495.
<https://www.ncbi.nlm.nih.gov/pubmed/22176867>
218. Rosenblatt, R., *et al.* Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. *Eur Urol*, 2012. 61: 1229.
<https://www.ncbi.nlm.nih.gov/pubmed/22189383>
219. Takata, R., *et al.* Predicting response to methotrexate, vinblastine, doxorubicin, and cisplatin neoadjuvant chemotherapy for bladder cancers through genome-wide gene expression profiling. *Clin Cancer Res*, 2005. 11: 2625.
<https://www.ncbi.nlm.nih.gov/pubmed/15814643>
220. Takata, R., *et al.* Validation study of the prediction system for clinical response of M-VAC neoadjuvant chemotherapy. *Cancer Sci*, 2007. 98: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/17116130>
221. Wallace, D.M., *et al.* Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. *Br J Urol*, 1991. 67: 608.
<https://www.ncbi.nlm.nih.gov/pubmed/2070206>
222. Font A, *et al.* Improved survival with induction chemotherapy in bladder cancer: preliminary results of a randomized trial. *Ann Oncol* 1994. 5: Abstr #355. [No abstract available].
223. Martinez-Pineiro, J.A., *et al.* Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. *J Urol*, 1995. 153: 964.
<https://www.ncbi.nlm.nih.gov/pubmed/7853584>

224. Rintala, E., *et al.* Neoadjuvant chemotherapy in bladder cancer: a randomized study. *Nordic Cystectomy Trial I. Scand J Urol Nephrol*, 1993. 27: 355.
<https://www.ncbi.nlm.nih.gov/pubmed/8290916>
225. Malmstrom, P.U., *et al.* Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. *J Urol*, 1996. 155: 1903.
<https://www.ncbi.nlm.nih.gov/pubmed/8618283>
226. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. *Lancet*, 1999. 354: 533.
<https://www.ncbi.nlm.nih.gov/pubmed/10470696>
227. Yuh, B.E., *et al.* Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. *J Urol*, 2013. 189: 1682.
<https://www.ncbi.nlm.nih.gov/pubmed/23123547>
228. Lee, F.C., *et al.* Pathologic Response Rates of Gemcitabine/Cisplatin versus Methotrexate/Vinblastine/Adriamycin/Cisplatin Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Bladder Cancer. *Adv Urol*, 2013. 2013: 317190.
<https://www.ncbi.nlm.nih.gov/pubmed/24382958>
229. Dash, A., *et al.* A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer*, 2008. 113: 2471.
<https://www.ncbi.nlm.nih.gov/pubmed/18823036>
230. Weight, C.J., *et al.* Lack of pathologic down-staging with neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder: a contemporary series. *Cancer*, 2009. 115: 792.
<https://www.ncbi.nlm.nih.gov/pubmed/19127557>
231. Zaghloul, M.S. The need to revisit adjuvant and neoadjuvant radiotherapy in bladder cancer. *Expert Rev Anticancer Ther*, 2010. 10: 1527.
<https://www.ncbi.nlm.nih.gov/pubmed/20942623>
232. El-Monim, H.A., *et al.* A prospective randomized trial for postoperative vs. preoperative adjuvant radiotherapy for muscle-invasive bladder cancer. *Urol Oncol*, 2013. 31: 359.
<https://www.ncbi.nlm.nih.gov/pubmed/21353794>
233. Bayoumi, Y., *et al.* Survival benefit of adjuvant radiotherapy in stage III and IV bladder cancer: results of 170 patients. *Cancer Manag Res*, 2014. 6: 459.
<https://www.ncbi.nlm.nih.gov/pubmed/25506244>
234. Widmark, A., *et al.* A systematic overview of radiation therapy effects in urinary bladder cancer. *Acta Oncol*, 2003. 42: 567.
<https://www.ncbi.nlm.nih.gov/pubmed/14596515>
235. Diaz, D.A., *et al.* Neoadjuvant Radiotherapy Improves Survival in Patients With T2b/T3 Bladder Cancer: A Population-Based Analysis. *Clin Genitourin Cancer*, 2015. 13: 378.
<https://www.ncbi.nlm.nih.gov/pubmed/25907230>
236. Granfors, T., *et al.* Downstaging and survival benefits of neoadjuvant radiotherapy before cystectomy for patients with invasive bladder carcinoma. *Scand J Urol Nephrol*, 2009. 43: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/19363744>
237. Slack, N.H., *et al.* Five-year follow-up results of a collaborative study of therapies for carcinoma of the bladder. *J Surg Oncol*, 1977. 9: 393.
<https://www.ncbi.nlm.nih.gov/pubmed/330958>
238. Smith, J.A., Jr., *et al.* Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: a phase III intergroup study. *J Urol*, 1997. 157: 805.
<https://www.ncbi.nlm.nih.gov/pubmed/9072571>
239. Ghoneim, M.A., *et al.* Randomized trial of cystectomy with or without preoperative radiotherapy for carcinoma of the bilharzial bladder. *J Urol*, 1985. 134: 266.
<https://www.ncbi.nlm.nih.gov/pubmed/3894693>
240. Anderstrom, C., *et al.* A prospective randomized study of preoperative irradiation with cystectomy or cystectomy alone for invasive bladder carcinoma. *Eur Urol*, 1983. 9: 142.
<https://www.ncbi.nlm.nih.gov/pubmed/6861819>
241. Blackard, C.E., *et al.* Results of a clinical trial of surgery and radiation in stages II and 3 carcinoma of the bladder. *J Urol*, 1972. 108: 875.
<https://www.ncbi.nlm.nih.gov/pubmed/5082739>
242. Huncharek, M., *et al.* Planned preoperative radiation therapy in muscle invasive bladder cancer; results of a meta-analysis. *Anticancer Res*, 1998. 18: 1931.
<https://www.ncbi.nlm.nih.gov/pubmed/9677446>

243. Hautmann, R.E., *et al.* Urinary diversion. *Urology*, 2007. 69: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/17280907>
244. Figueroa, A.J., *et al.* Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. *Cancer*, 1998. 83: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/9655304>
245. Geriatric Assessment Methods for Clinical Decision making. NIH Consensus Statement Online N.I.o. Health, Editor. 1987, U.S. Department of Health & Human Services.
246. Nielsen, M.E., *et al.* A delay in radical cystectomy of >3 months is not associated with a worse clinical outcome. *BJU Int*, 2007. 100: 1015.
<https://www.ncbi.nlm.nih.gov/pubmed/17784888>
247. Ayres, B.E., *et al.* A delay in radical cystectomy of >3 months is not associated with a worse clinical outcome. *BJU Int*, 2008. 102: 1045.
<https://www.ncbi.nlm.nih.gov/pubmed/18840144>
248. Gore, J.L., *et al.* Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results-Medicare analysis. *Cancer*, 2009. 115: 988.
<https://www.ncbi.nlm.nih.gov/pubmed/19142878>
249. Le Bret, T., *et al.* After cystectomy, is it justified to perform a bladder replacement for patients with lymph node positive bladder cancer? *Eur Urol*, 2002. 42: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/12361899>
250. Mertens, L.S., *et al.* Prostate sparing cystectomy for bladder cancer: 20-year single center experience. *J Urol*, 2014. 191: 1250.
<https://www.ncbi.nlm.nih.gov/pubmed/24286830>
251. Stenzl, A., *et al.* Cystectomy - Technical Considerations in Male and Female Patients. *EAU Update Series*, 2005. 3: 138.
<http://www.sciencedirect.com/science/article/pii/S1570912405000310?np=y>
252. Wallmeroth, A., *et al.* Patterns of metastasis in muscle-invasive bladder cancer (pT2-4): An autopsy study on 367 patients. *Urol Int*, 1999. 62: 69.
<https://www.ncbi.nlm.nih.gov/pubmed/10461106>
253. Davies, J.D., *et al.* Anatomic basis for lymph node counts as measure of lymph node dissection extent: a cadaveric study. *Urology*, 2013. 81: 358.
<https://www.ncbi.nlm.nih.gov/pubmed/23374802>
254. Jensen, J.B., *et al.* Lymph node mapping in patients with bladder cancer undergoing radical cystectomy and lymph node dissection to the level of the inferior mesenteric artery. *BJU Int*, 2010. 106: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/20002670>
255. Vazina, A., *et al.* Stage specific lymph node metastasis mapping in radical cystectomy specimens. *J Urol*, 2004. 171: 1830.
<https://www.ncbi.nlm.nih.gov/pubmed/15076287>
256. Leissner, J., *et al.* Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol*, 2004. 171: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/14665862>
257. Roth, B., *et al.* A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder. *Eur Urol*, 2010. 57: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/19879039>
258. Dorin, R.P., *et al.* Lymph node dissection technique is more important than lymph node count in identifying nodal metastases in radical cystectomy patients: a comparative mapping study. *Eur Urol*, 2011. 60: 946.
<https://www.ncbi.nlm.nih.gov/pubmed/21802833>
259. Wiesner, C., *et al.* Cancer-specific survival after radical cystectomy and standardized extended lymphadenectomy for node-positive bladder cancer: prediction by lymph node positivity and density. *BJU Int*, 2009. 104: 331.
<https://www.ncbi.nlm.nih.gov/pubmed/19220265>
260. Simone, G., *et al.* Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. *Int J Urol*, 2013. 20: 390.
<https://www.ncbi.nlm.nih.gov/pubmed/22970939>
261. Holmer, M., *et al.* Extended lymph node dissection in patients with urothelial cell carcinoma of the bladder: can it make a difference? *World J Urol*, 2009. 27: 521.
<https://www.ncbi.nlm.nih.gov/pubmed/19145436>

262. Poulsen, A.L., *et al.* Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. *J Urol*, 1998. 160: 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/9817313>
263. Jensen, J.B., *et al.* Extended versus limited lymph node dissection in radical cystectomy: impact on recurrence pattern and survival. *Int J Urol*, 2012. 19: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/22050425>
264. Dhar, N.B., *et al.* Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. *J Urol*, 2008. 179: 873.
<https://www.ncbi.nlm.nih.gov/pubmed/18221953>
265. Zlotta, A.R. Limited, extended, superextended, megaextended pelvic lymph node dissection at the time of radical cystectomy: what should we perform? *Eur Urol*, 2012. 61: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/22119158>
266. Zehnder, P., *et al.* Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. *J Urol*, 2011. 186: 1261.
<https://www.ncbi.nlm.nih.gov/pubmed/21849183>
267. Bruins, H.M., *et al.* The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. *Eur Urol*, 2014. 66: 1065.
<https://www.ncbi.nlm.nih.gov/pubmed/25074764>
268. Brossner, C., *et al.* Does extended lymphadenectomy increase the morbidity of radical cystectomy? *BJU Int*, 2004. 93: 64.
<https://www.ncbi.nlm.nih.gov/pubmed/14678370>
269. Finelli, A., *et al.* Laparoscopic extended pelvic lymphadenectomy for bladder cancer: technique and initial outcomes. *J Urol*, 2004. 172: 1809.
<https://www.ncbi.nlm.nih.gov/pubmed/15540725>
270. Abd El Latif, A., *et al.* 1752 Impact of extended versus standard lymph node dissection on overall survival among patients with urothelial cancer of bladder. *J Urol*. 187: e707.
[http://www.jurology.com/article/S0022-5347\(12\)02130-1/abstract](http://www.jurology.com/article/S0022-5347(12)02130-1/abstract)
271. Abd El Latif, A., *et al.* 1896. Impact of extended versus standard lymph node dissection (SLND) on post-cystectomy survival (PCS) among patients with LN-negative urothelial bladder cancer (UBC). *J Urol*. 185: e759.
[http://www.jurology.com/article/S0022-5347\(11\)02268-3/abstract](http://www.jurology.com/article/S0022-5347(11)02268-3/abstract)
272. Abol-Enein, H., *et al.* Does the extent of lymphadenectomy in radical cystectomy for bladder cancer influence disease-free survival? A prospective single-center study. *Eur Urol*, 2011. 60: 572.
<https://www.ncbi.nlm.nih.gov/pubmed/21684070>
273. Dharaskar, A., *et al.* Does extended lymph node dissection affect the lymph node density and survival after radical cystectomy? *Indian J Cancer*, 2011. 48: 230.
<https://www.ncbi.nlm.nih.gov/pubmed/21768672>
274. Abdollah, F., *et al.* Stage-specific impact of pelvic lymph node dissection on survival in patients with non-metastatic bladder cancer treated with radical cystectomy. *BJU Int*, 2012. 109: 1147.
<https://www.ncbi.nlm.nih.gov/pubmed/21883849>
275. Liu, J.-J., *et al.* 1404. Practice patterns of pelvic lymph node dissection for radical cystectomy from the Veterans Affairs Central Cancer Registry (VACCR). *J Urol*. 185: e562.
[http://www.jurology.com/article/S0022-5347\(11\)01543-6/abstract](http://www.jurology.com/article/S0022-5347(11)01543-6/abstract)
276. Isaka, S., *et al.* [Pelvic lymph node dissection for invasive bladder cancer]. *Nihon Hinyokika Gakkai Zasshi*, 1989. 80: 402.
<https://www.ncbi.nlm.nih.gov/pubmed/2733302>
277. Miyakawa, M., *et al.* [Results of the multidisciplinary treatment of invasive bladder cancer]. *Hinyokika Kyo*, 1986. 32: 1931.
<https://www.ncbi.nlm.nih.gov/pubmed/3825830>
278. Simone, G., *et al.* 1755. Extended versus super-extended PLND during radical cystectomy: comparison of two prospective series. *J Urol*. 187: e708.
[http://www.jurology.com/article/S0022-5347\(12\)02133-7/abstract](http://www.jurology.com/article/S0022-5347(12)02133-7/abstract)
279. Bostrom, P.J., *et al.* 1595. Extended lymphadenectomy and chemotherapy and chemotherapy offer survival advantage in muscle-invasive bladder cancer. *J Urol*. 185: e640.
[http://www.jurology.com/article/S0022-5347\(11\)01893-3/abstract](http://www.jurology.com/article/S0022-5347(11)01893-3/abstract)

280. Yuasa, M., *et al.* [Clinical evaluation of total cystectomy for bladder carcinoma: a ten-year experience]. *Hinyokika Kyo*, 1988. 34: 975.
<https://www.ncbi.nlm.nih.gov/pubmed/3223462>
281. Mandel, P., *et al.* Extent of lymph node dissection and recurrence-free survival after radical cystectomy: a meta-analysis. *Urol Oncol*, 2014. 32: 1184.
<https://www.ncbi.nlm.nih.gov/pubmed/25027683>
282. Bi, L., *et al.* Extended vs non-extended pelvic lymph node dissection and their influence on recurrence-free survival in patients undergoing radical cystectomy for bladder cancer: a systematic review and meta-analysis of comparative studies. *BJU Int*, 2014. 113: E39.
<https://www.ncbi.nlm.nih.gov/pubmed/24053715>
283. Koppie, T.M., *et al.* Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? *Cancer*, 2006. 107: 2368.
<https://www.ncbi.nlm.nih.gov/pubmed/17041887>
284. Fleischmann, A., *et al.* Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. *J Clin Oncol*, 2005. 23: 2358.
<https://www.ncbi.nlm.nih.gov/pubmed/15800327>
285. Wright, J.L., *et al.* The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. *Cancer*, 2008. 112: 2401.
<https://www.ncbi.nlm.nih.gov/pubmed/18383515>
286. Studer, U.E., *et al.* Morbidity from pelvic lymphadenectomy in men undergoing radical prostatectomy. *Eur Urol*, 2006. 50: 887.
<https://www.ncbi.nlm.nih.gov/pubmed/16956714>
287. Hernandez V., *et al.* What are the oncological and functional outcomes of sexual-function preserving cystectomy compared with standard radical cystectomy in men with bladder cancer? PROSPERO International prospective register of systematic reviews, 2015.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020742
288. Kessler, T.M., *et al.* Attempted nerve sparing surgery and age have a significant effect on urinary continence and erectile function after radical cystoprostatectomy and ileal orthotopic bladder substitution. *J Urol*, 2004. 172: 1323.
<https://www.ncbi.nlm.nih.gov/pubmed/15371833>
289. de Vries, R.R., *et al.* Prostate-sparing cystectomy: long-term oncological results. *BJU Int*, 2009. 104: 1239.
<https://www.ncbi.nlm.nih.gov/pubmed/24286830>
290. Basiri, A., *et al.* Overall survival and functional results of prostate-sparing cystectomy: a matched case-control study. *Urol J*, 2012. 9: 678.
<https://www.ncbi.nlm.nih.gov/pubmed/23235973>
291. Wang, X.H., *et al.* [Impact of preservation of distal prostatic capsula and seminal vesicle on functions of orthotopic ideal neobladder and erectile function of bladder cancer patients]. *Ai Zheng*, 2008. 27: 62.
<https://www.ncbi.nlm.nih.gov/pubmed/18184466>
292. Moon, H., *et al.* Nerve and Seminal Sparing Cystectomy for Bladder Cancer. *Korean J Urol* 2005; 555. [No abstract available].
293. Vilaseca, A., *et al.* Erectile function after cystectomy with neurovascular preservation. *Actas Urol Esp*, 2013. 37: 554.
<https://www.ncbi.nlm.nih.gov/pubmed/23790714>
294. el-Bahnasawy, M.S., *et al.* Urethral pressure profile following orthotopic neobladder: differences between nerve sparing and standard radical cystectomy techniques. *J Urol*, 2006. 175: 1759.
<https://www.ncbi.nlm.nih.gov/pubmed/16600753>
295. Hekal, I.A., *et al.* Recoverability of erectile function in post-radical cystectomy patients: subjective and objective evaluations. *Eur Urol*, 2009. 55: 275.
<https://www.ncbi.nlm.nih.gov/pubmed/18603350>
296. Jacobs, B.L., *et al.* Prostate capsule sparing versus nerve sparing radical cystectomy for bladder cancer: results of a randomized, controlled trial. *J Urol*, 2015. 193: 64.
<https://www.ncbi.nlm.nih.gov/pubmed/25066875>
297. Colombo, R., *et al.* Fifteen-year single-centre experience with three different surgical procedures of nerve-sparing cystectomy in selected organ-confined bladder cancer patients. *World J Urol*, 2015. 33: 1389.
<https://www.ncbi.nlm.nih.gov/pubmed/25577131>

298. Gotsadze, D.T., *et al.* [Why and how to modify standard cystectomy]. *Urologiia*, 2008: 22.
<https://www.ncbi.nlm.nih.gov/pubmed/18572764>
299. Rozet F, L.G., Cathelineau X, *et al.* Oncological evaluation of prostate sparing cystectomy: the Montsouris long-term results. *J Urol*, 2008. 179.
<https://www.ncbi.nlm.nih.gov/pubmed/18572764>
300. Muto, G., *et al.* Seminal-sparing cystectomy: technical evolution and results over a 20-year period. *Urology*, 2014. 83: 856.
<https://www.ncbi.nlm.nih.gov/pubmed/24485363>
301. Veskimae, E., *et al.* Systematic review of the oncological and functional outcomes of pelvic organ-preserving cystectomy compared with standard radical cystectomy in women who undergo curative surgery and orthotopic neobladder substitution for bladder cancer. *BJU Int*, 2017. DOI: 10.1111/bju.13819.
302. Novara, G., *et al.* Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. *Eur Urol*, 2015. 67: 376.
<https://www.ncbi.nlm.nih.gov/pubmed/25560797>
303. Wilson, T.G., *et al.* Best practices in robot-assisted radical cystectomy and urinary reconstruction: recommendations of the Pasadena Consensus Panel. *Eur Urol*, 2015. 67: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/25582930>
304. Bochner, B.H., *et al.* Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: A Randomized Clinical Trial. *Eur Urol*, 2015. 67: 1042.
<https://www.ncbi.nlm.nih.gov/pubmed/25496767>
305. Yuh, B., *et al.* Systematic review and cumulative analysis of oncologic and functional outcomes after robot-assisted radical cystectomy. *Eur Urol*, 2015. 67: 402.
<https://www.ncbi.nlm.nih.gov/pubmed/25560797>
306. Nguyen, D.P., *et al.* Recurrence patterns after open and robot-assisted radical cystectomy for bladder cancer. *Eur Urol*, 2015. 68: 399.
<https://www.ncbi.nlm.nih.gov/pubmed/25709026>
307. Fahmy, O., *et al.* Current status of robotic assisted radical cystectomy with intracorporeal ileal neobladder for bladder cancer. *J Surg Oncol*, 2015. 112: 427.
<https://www.ncbi.nlm.nih.gov/pubmed/26265262>
308. Tang, K., *et al.* Laparoscopic versus open radical cystectomy in bladder cancer: a systematic review and meta-analysis of comparative studies. *PLoS One*, 2014. 9: e95667.
<https://www.ncbi.nlm.nih.gov/pubmed/24835573>
309. Stenzl, A. Bladder substitution. *Curr Opin Urol*, 1999. 9: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/10726098>
310. de Vries, R.R., *et al.* Short-term outcome after cystectomy: comparison of two different perioperative protocols. *Urol Int*, 2012. 88: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/22433508>
311. Malavaud, B., *et al.* Complications for radical cystectomy. Impact of the American Society of Anesthesiologists score. *Eur Urol*, 2001. 39: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/11173943>
312. Haynes, S.R., *et al.* An assessment of the consistency of ASA physical status classification allocation. *Anaesthesia*, 1995. 50: 195.
<https://www.ncbi.nlm.nih.gov/pubmed/7717481>
313. Azimuddin, K., *et al.* Neoplasia after ureterosigmoidostomy. *Dis Colon Rectum*, 1999. 42: 1632.
<https://www.ncbi.nlm.nih.gov/pubmed/10613486>
314. Gerharz, E.W., *et al.* Metabolic and functional consequences of urinary reconstruction with bowel. *BJU Int*, 2003. 91: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/12519116>
315. Madersbacher, S., *et al.* Contemporary cystectomy and urinary diversion. *World J Urol*, 2002. 20: 151.
<https://www.ncbi.nlm.nih.gov/pubmed/12196898>
316. Pruthi, R.S., *et al.* Fast track program in patients undergoing radical cystectomy: results in 362 consecutive patients. *J Am Coll Surg*, 2010. 210: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/20123338>
317. Kouba, E.J., *et al.* Gum chewing stimulates bowel motility in patients undergoing radical cystectomy with urinary diversion. *Urology*, 2007. 70: 1053.
<https://www.ncbi.nlm.nih.gov/pubmed/18158012>

318. Karl, A., *et al.* A new concept for early recovery after surgery for patients undergoing radical cystectomy for bladder cancer: results of a prospective randomized study. *J Urol*, 2014. 191: 335. <https://www.ncbi.nlm.nih.gov/pubmed/23968966>
319. Xu, W., *et al.* Postoperative Pain Management after Radical Cystectomy: Comparing Traditional versus Enhanced Recovery Protocol Pathway. *J Urol*, 2015. 194: 1209. <https://www.ncbi.nlm.nih.gov/pubmed/26021824>
320. Lee, C.T., *et al.* Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. *Eur Urol*, 2014. 66: 265. <https://www.ncbi.nlm.nih.gov/pubmed/24630419>
321. Hautmann, R.E., *et al.* Long-term results of standard procedures in urology: the ileal neobladder. *World J Urol*, 2006. 24: 305. <https://www.ncbi.nlm.nih.gov/pubmed/20643429>
322. Hautmann, R.E., *et al.* Lessons learned from 1,000 neobladders: the 90-day complication rate. *J Urol*, 2010. 184: 990. <https://www.ncbi.nlm.nih.gov/pubmed/20643429>
323. Stein, J.P., *et al.* Indications and technique of the orthotopic neobladder in women. *Urol Clin North Am*, 2002. 29: 725. <https://www.ncbi.nlm.nih.gov/pubmed/12476536>
324. Hautmann, R.E., *et al.* Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. *Eur Urol*, 2012. 61: 1039. <https://www.ncbi.nlm.nih.gov/pubmed/22381169>
325. Jentzmik, F., *et al.* The ileal neobladder in female patients with bladder cancer: long-term clinical, functional, and oncological outcome. *World J Urol*, 2012. 30: 733. <https://www.ncbi.nlm.nih.gov/pubmed/22322390>
326. Ahmadi, H., *et al.* Urinary functional outcome following radical cystoprostatectomy and ileal neobladder reconstruction in male patients. *J Urol*, 2013. 189: 1782. <https://www.ncbi.nlm.nih.gov/pubmed/23159582>
327. Neuzillet, Y., *et al.* The Z-shaped ileal neobladder after radical cystectomy: an 18 years experience with 329 patients. *BJU Int*, 2011. 108: 596. <https://www.ncbi.nlm.nih.gov/pubmed/21223470>
328. Gershman, B., *et al.* Comparative impact of continent and incontinent urinary diversion on long-term renal function after radical cystectomy in patients with preoperative chronic kidney disease 2 and chronic kidney disease 3a. *Int J Urol*, 2015. 22: 651. <https://www.ncbi.nlm.nih.gov/pubmed/25881721>
329. Longo, N., *et al.* Complications and quality of life in elderly patients with several comorbidities undergoing cutaneous ureterostomy with single stoma or ileal conduit after radical cystectomy. *BJU Int*, 2016. 118: 521. <https://www.ncbi.nlm.nih.gov/pubmed/26935245>
330. Deliveliotis, C., *et al.* Urinary diversion in high-risk elderly patients: modified cutaneous ureterostomy or ileal conduit? *Urology*, 2005. 66: 299. <https://www.ncbi.nlm.nih.gov/pubmed/16040096>
331. Kilciler, M., *et al.* Comparison of ileal conduit and transureteroureterostomy with ureterocutaneostomy urinary diversion. *Urol Int*, 2006. 77: 245. <https://www.ncbi.nlm.nih.gov/pubmed/17033213>
332. Berger, I., *et al.* Impact of the use of bowel for urinary diversion on perioperative complications and 90-day mortality in patients aged 75 years or older. *Urol Int*, 2015. 94: 394. <https://www.ncbi.nlm.nih.gov/pubmed/25612612>
333. Nieuwenhuijzen, J.A., *et al.* Urinary diversions after cystectomy: the association of clinical factors, complications and functional results of four different diversions. *Eur Urol*, 2008. 53: 834. <https://www.ncbi.nlm.nih.gov/pubmed/17904276>
334. Madersbacher, S., *et al.* Long-term outcome of ileal conduit diversion. *J Urol*, 2003. 169: 985. <https://www.ncbi.nlm.nih.gov/pubmed/12576827>
335. Wood, D.N., *et al.* Stomal complications of ileal conduits are significantly higher when formed in women with intractable urinary incontinence. *J Urol*, 2004. 172: 2300. <https://www.ncbi.nlm.nih.gov/pubmed/15538253>
336. Neal, D.E. Complications of ileal conduit diversion in adults with cancer followed up for at least five years. *Br Med J (Clin Res Ed)*, 1985. 290: 1695. <https://www.ncbi.nlm.nih.gov/pubmed/3924218>

337. Mues, A.C., *et al.* Contemporary experience in the management of angiomyolipoma. *J Endourol*, 2010. 24: 1883.
<https://www.ncbi.nlm.nih.gov/pubmed/20919915>
338. Benson, M.C., *et al.* Continent urinary diversion. *Urol Clin North Am*, 1999. 26: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/10086055>
339. Gerharz, E.W., *et al.* Ten years' experience with the submucosally embedded *in situ* appendix in continent cutaneous diversion. *Eur Urol*, 2001. 40: 625.
<https://www.ncbi.nlm.nih.gov/pubmed/11805408>
340. Jonsson, O., *et al.* Long-time experience with the Kock ileal reservoir for continent urinary diversion. *Eur Urol*, 2001. 40: 632.
<https://www.ncbi.nlm.nih.gov/pubmed/11805409>
341. Thoeny, H.C., *et al.* Is ileal orthotopic bladder substitution with an afferent tubular segment detrimental to the upper urinary tract in the long term? *J Urol*, 2002. 168: 2030.
<https://www.ncbi.nlm.nih.gov/pubmed/11834389>
342. Wiesner, C., *et al.* Continent cutaneous urinary diversion: long-term follow-up of more than 800 patients with ileocecal reservoirs. *World J Urol*, 2006. 24: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/16676186>
343. Wiesner, C., *et al.* Long-term followup of the intussuscepted ileal nipple and the *in situ*, submucosally embedded appendix as continence mechanisms of continent urinary diversion with the cutaneous ileocecal pouch (Mainz pouch I). *J Urol*, 2006. 176: 155.
<https://www.ncbi.nlm.nih.gov/pubmed/16753391>
344. Leissner, J., *et al.* Colon pouch (Mainz pouch III) for continent urinary diversion after pelvic irradiation. *Urology*, 2000. 56: 798.
<https://www.ncbi.nlm.nih.gov/pubmed/11068305>
345. Simon, J. Ectopia Vesicae (Absence of the anterior walls of the Bladder and the pubic abdominal parietes) Operation for directing the orifices of the ureteres into the rectum, temporary success) *JAMA* 1911. 1911: 398. [No abstract available].
346. Coffey, R.C. Physiologic implantation of the severed ureter or common bile-duct into the intestine. *JAMA*, 1911. LVI: 397.
<http://dx.doi.org/10.1001/jama.1911.02560060007002>
347. Kalble, T., *et al.* Tumor induction and prophylaxis following different forms of intestinal urinary diversion in a rat model. *Urol Res*, 1995. 23: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/8788273>
348. Donat, S.M., *et al.* Radical cystectomy in octogenarians--does morbidity outweigh the potential survival benefits? *J Urol*, 2010. 183: 2171.
<https://www.ncbi.nlm.nih.gov/pubmed/20399461>
349. Hautmann, R.E., *et al.* 25 years of experience with 1,000 neobladders: long-term complications. *J Urol*, 2011. 185: 2207.
<https://www.ncbi.nlm.nih.gov/pubmed/21497841>
350. Stein, J.P., *et al.* The orthotopic T pouch ileal neobladder: experience with 209 patients. *J Urol*, 2004. 172: 584.
<https://www.ncbi.nlm.nih.gov/pubmed/15247737>
351. Abol-Enein, H., *et al.* Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. *J Urol*, 2001. 165: 1427.
<https://www.ncbi.nlm.nih.gov/pubmed/11342891>
352. Stein, J.P., *et al.* Results with radical cystectomy for treating bladder cancer: a 'reference standard' for high-grade, invasive bladder cancer. *BJU Int*, 2003. 92: 12.
<https://www.ncbi.nlm.nih.gov/pubmed/12823375>
353. Yossepowitch, O., *et al.* Orthotopic urinary diversion after cystectomy for bladder cancer: implications for cancer control and patterns of disease recurrence. *J Urol*, 2003. 169: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/12478130>
354. Stein, J.P., *et al.* Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. *J Urol*, 2005. 173: 1163.
<https://www.ncbi.nlm.nih.gov/pubmed/15758728>
355. Gerharz, E.W., *et al.* Quality of life after cystectomy and urinary diversion: an evidence based analysis. *J Urol*, 2005. 174: 1729.
<https://www.ncbi.nlm.nih.gov/pubmed/16217273>
356. Hobisch, A., *et al.* Life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. *Semin Urol Oncol*, 2001. 19: 18.
<https://www.ncbi.nlm.nih.gov/pubmed/11246729>

357. Porter, M.P., *et al.* Health related quality of life after radical cystectomy and urinary diversion for bladder cancer: a systematic review and critical analysis of the literature. *J Urol*, 2005. 173: 1318. <https://www.ncbi.nlm.nih.gov/pubmed/15758789>
358. Gakis, G., *et al.* [Benefits and risks of orthotopic neobladder reconstruction in female patients]. *Aktuelle Urol*, 2011. 42: 109. <https://www.ncbi.nlm.nih.gov/pubmed/21437834>
359. Stein, J.P., *et al.* Pathological guidelines for orthotopic urinary diversion in women with bladder cancer: a review of the literature. *J Urol*, 2007. 178: 756. <https://www.ncbi.nlm.nih.gov/pubmed/17631333>
360. Stein, J.P., *et al.* Indications for lower urinary tract reconstruction in women after cystectomy for bladder cancer: a pathological review of female cystectomy specimens. *J Urol*, 1995. 154: 1329. <https://www.ncbi.nlm.nih.gov/pubmed/7658531>
361. Vallancien, G., *et al.* Cystectomy with prostate sparing for bladder cancer in 100 patients: 10-year experience. *J Urol*, 2002. 168: 2413. <https://www.ncbi.nlm.nih.gov/pubmed/12441929>
362. Stenzl, A., *et al.* Radical cystectomy with orthotopic neobladder for invasive bladder cancer: a critical analysis of long term oncological, functional and quality of life results. *Int Braz J Urol*, 2010. 36: 537. <https://www.ncbi.nlm.nih.gov/pubmed/21044370>
363. Nielsen, M.E., *et al.* Association of hospital volume with conditional 90-day mortality after cystectomy: an analysis of the National Cancer Data Base. *BJU Int*, 2014. 114: 46. <https://www.ncbi.nlm.nih.gov/pubmed/24219110>
364. Porter, M.P., *et al.* Hospital volume and 90-day mortality risk after radical cystectomy: a population-based cohort study. *World J Urol*, 2011. 29: 73. <https://www.ncbi.nlm.nih.gov/pubmed/21132553>
365. Hautmann, R.E., *et al.* ICUD-EAU International Consultation on Bladder Cancer 2012: Urinary diversion. *Eur Urol*, 2013. 63: 67. <https://www.ncbi.nlm.nih.gov/pubmed/22995974>
366. Cookson, M.S., *et al.* Complications of radical cystectomy for nonmuscle invasive disease: comparison with muscle invasive disease. *J Urol*, 2003. 169: 101. <https://www.ncbi.nlm.nih.gov/pubmed/12478113>
367. Sabir, E.F., *et al.* Impact of hospital volume on local recurrence and distant metastasis in bladder cancer patients treated with radical cystectomy in Sweden. *Scand J Urol*, 2013. 47: 483. <https://www.ncbi.nlm.nih.gov/pubmed/23590830>
368. Morgan, T.M., *et al.* Volume outcomes of cystectomy--is it the surgeon or the setting? *J Urol*, 2012. 188: 2139. <https://www.ncbi.nlm.nih.gov/pubmed/23083864>
369. Finks, J.F., *et al.* Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med*, 2011. 364: 2128. <https://www.ncbi.nlm.nih.gov/pubmed/21631325>
370. Corcoran, A.T., *et al.* Variation in performance of candidate surgical quality measures for muscle-invasive bladder cancer by hospital type. *BJU Int*, 2015. 115: 230. <https://www.ncbi.nlm.nih.gov/pubmed/24447637>
371. Ravi, P., *et al.* Benefit in regionalisation of care for patients treated with radical cystectomy: a nationwide inpatient sample analysis. *BJU Int*, 2014. 113: 733. <https://www.ncbi.nlm.nih.gov/pubmed/24007240>
372. Shabsigh, A., *et al.* Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol*, 2009. 55: 164. <https://www.ncbi.nlm.nih.gov/pubmed/18675501>
373. Wang, Y.L., *et al.* Perioperative Blood Transfusion Promotes Worse Outcomes of Bladder Cancer after Radical Cystectomy: A Systematic Review and Meta-Analysis. *PLoS One*, 2015. 10: e0130122. <https://www.ncbi.nlm.nih.gov/pubmed/26080092>
374. Zaid, H.B., *et al.* Efficacy and Safety of Intraoperative Tranexamic Acid Infusion for Reducing Blood Transfusion During Open Radical Cystectomy. *Urology*, 2016. 92: 57. <https://www.ncbi.nlm.nih.gov/pubmed/26968489>
375. Hammond, J., *et al.* Rates of venous thromboembolism among patients with major surgery for cancer. *Ann Surg Oncol*, 2011. 18: 3240. <https://www.ncbi.nlm.nih.gov/pubmed/21584837>

376. Potretzke, A.M., *et al.* Highest risk of symptomatic venous thromboembolic events after radical cystectomy occurs in patients with obesity or nonurothelial cancers. *Urol Ann*, 2015. 7: 355.
<https://www.ncbi.nlm.nih.gov/pubmed/26229325>
377. Shariat, S.F., *et al.* Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol*, 2006. 176: 2414.
<https://www.ncbi.nlm.nih.gov/pubmed/17085118>
378. Nuhn, P., *et al.* External validation of postoperative nomograms for prediction of all-cause mortality, cancer-specific mortality, and recurrence in patients with urothelial carcinoma of the bladder. *Eur Urol*, 2012. 61: 58.
<https://www.ncbi.nlm.nih.gov/pubmed/21840642>
379. Bruins, H.M., *et al.* Clinical outcomes and recurrence predictors of lymph node positive urothelial cancer after cystectomy. *J Urol*, 2009. 182: 2182.
<https://www.ncbi.nlm.nih.gov/pubmed/19758623>
380. Abdollah, F., *et al.* Incidence, survival and mortality rates of stage-specific bladder cancer in United States: a trend analysis. *Cancer Epidemiol*, 2013. 37: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/23485480>
381. Ok, J.H., *et al.* Medical and surgical palliative care of patients with urological malignancies. *J Urol*, 2005. 174: 1177.
<https://www.ncbi.nlm.nih.gov/pubmed/16145365>
382. Ubrig, B., *et al.* Extraperitoneal bilateral cutaneous ureterostomy with midline stoma for palliation of pelvic cancer. *Urology*, 2004. 63: 973.
<https://www.ncbi.nlm.nih.gov/pubmed/15134993>
383. Zebic, N., *et al.* Radical cystectomy in patients aged > or = 75 years: an updated review of patients treated with curative and palliative intent. *BJU Int*, 2005. 95: 1211.
<https://www.ncbi.nlm.nih.gov/pubmed/15892803>
384. El-Tabey, N.A., *et al.* Bladder cancer with obstructive uremia: oncologic outcome after definitive surgical management. *Urology*, 2005. 66: 531.
<https://www.ncbi.nlm.nih.gov/pubmed/16140072>
385. Nagele, U., *et al.* The rationale for radical cystectomy as primary therapy for T4 bladder cancer. *World J Urol*, 2007. 25: 401.
<https://www.ncbi.nlm.nih.gov/pubmed/17525849>
386. Ghahestani, S.M., *et al.* Palliative treatment of intractable hematuria in context of advanced bladder cancer: a systematic review. *Urol J*, 2009. 6: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/19711266>
387. Srinivasan, V., *et al.* A comparison of two radiotherapy regimens for the treatment of symptoms from advanced bladder cancer. *Clin Oncol (R Coll Radiol)*, 1994. 6: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/7513538>
388. Herr, H.W. Conservative management of muscle-infiltrating bladder cancer: prospective experience. *J Urol*, 1987. 138: 1162.
<https://www.ncbi.nlm.nih.gov/pubmed/3669160>
389. Herr, H.W. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. *J Clin Oncol*, 2001. 19: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/11134199>
390. Holmang, S., *et al.* Long-term followup of all patients with muscle invasive (stages T2, T3 and T4) bladder carcinoma in a geographical region. *J Urol*, 1997. 158: 389.
<https://www.ncbi.nlm.nih.gov/pubmed/9224309>
391. Solsona, E., *et al.* Feasibility of radical transurethral resection as monotherapy for selected patients with muscle invasive bladder cancer. *J Urol*, 2010. 184: 475.
<https://www.ncbi.nlm.nih.gov/pubmed/20620402>
392. Whitmore, W.F., Jr., *et al.* Radical cystectomy with or without prior irradiation in the treatment of bladder cancer. *J Urol*, 1977. 118: 184.
<https://www.ncbi.nlm.nih.gov/pubmed/875217>
393. Milosevic, M., *et al.* Radiotherapy for bladder cancer. *Urology*, 2007. 69: 80.
<https://www.ncbi.nlm.nih.gov/pubmed/17280910>
394. Sondergaard, J., *et al.* A comparison of morbidity following conformal versus intensity-modulated radiotherapy for urinary bladder cancer. *Acta Oncol*, 2014. 53: 1321.
<https://www.ncbi.nlm.nih.gov/pubmed/24980045>
395. Tonoli, S., *et al.* Radical radiotherapy for bladder cancer: retrospective analysis of a series of 459 patients treated in an Italian institution. *Clin Oncol (R Coll Radiol)*, 2006. 18: 52.
<https://www.ncbi.nlm.nih.gov/pubmed/16477920>

396. Chung, P.W., *et al.* Long-term outcome of radiation-based conservation therapy for invasive bladder cancer. *Urol Oncol*, 2007. 25: 303.
<https://www.ncbi.nlm.nih.gov/pubmed/17628296>
397. Shelley, M.D., *et al.* Surgery versus radiotherapy for muscle invasive bladder cancer. *Cochrane Database Syst Rev*, 2002: Cd002079.
<https://www.ncbi.nlm.nih.gov/pubmed/11869621>
398. Booth, C.M., *et al.* Curative therapy for bladder cancer in routine clinical practice: a population-based outcomes study. *Clin Oncol (R Coll Radiol)*, 2014. 26: 506.
<https://www.ncbi.nlm.nih.gov/pubmed/24954284>
399. Scher, H.I., *et al.* Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion. *J Urol*, 1988. 139: 470.
<https://www.ncbi.nlm.nih.gov/pubmed/3343728>
400. Herr, H.W., *et al.* Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. *J Clin Oncol*, 1998. 16: 1298.
<https://www.ncbi.nlm.nih.gov/pubmed/9552029>
401. Kachnic, L.A., *et al.* Bladder preservation by combined modality therapy for invasive bladder cancer. *J Clin Oncol*, 1997. 15: 1022.
<https://www.ncbi.nlm.nih.gov/pubmed/9060542>
402. Als, A.B., *et al.* Long-term survival after gemcitabine and cisplatin in patients with locally advanced transitional cell carcinoma of the bladder: focus on supplementary treatment strategies. *Eur Urol*, 2007. 52: 478.
<https://www.ncbi.nlm.nih.gov/pubmed/17383078>
403. Sternberg, C.N., *et al.* M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol*, 1988. 139: 461.
<https://www.ncbi.nlm.nih.gov/pubmed/3343727>
404. Logothetis, C.J., *et al.* A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol*, 1990. 8: 1050.
<https://www.ncbi.nlm.nih.gov/pubmed/2189954>
405. Loehrer, P.J., Sr., *et al.* A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol*, 1992. 10: 1066.
<https://www.ncbi.nlm.nih.gov/pubmed/1607913>
406. Kaufman, D., *et al.* Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. *J Clin Oncol*, 2000. 18: 1921.
<https://www.ncbi.nlm.nih.gov/pubmed/10784633>
407. Stadler, W.M., *et al.* Long-term survival in phase II trials of gemcitabine plus cisplatin for advanced transitional cell cancer. *Urol Oncol*, 2002. 7: 153.
<https://www.ncbi.nlm.nih.gov/pubmed/12474531>
408. Moore, M.J., *et al.* Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*, 1999. 17: 2876.
<https://www.ncbi.nlm.nih.gov/pubmed/11001674>
409. Bajorin, D.F., *et al.* Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol*, 1999. 17: 3173.
<https://www.ncbi.nlm.nih.gov/pubmed/10506615>
410. Herr, H.W., *et al.* Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. *J Urol*, 2001. 165: 811.
<https://www.ncbi.nlm.nih.gov/pubmed/11176475>
411. Ploussard, G., *et al.* Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: a systematic review. *Eur Urol*, 2014. 66: 120.
<https://www.ncbi.nlm.nih.gov/pubmed/24613684>
412. James, N.D., *et al.* Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *New Engl J Med*, 2012. 366: 1477.
<https://www.ncbi.nlm.nih.gov/pubmed/22512481>
413. Krause, F.S., *et al.* 15-year survival rates after transurethral resection and radiochemotherapy or radiation in bladder cancer treatment. *Anticancer Res*, 2011. 31: 985.
<https://www.ncbi.nlm.nih.gov/pubmed/21498726>
414. Efsthathiou, J.A., *et al.* Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. *Eur Urol*, 2012. 61: 705.
<https://www.ncbi.nlm.nih.gov/pubmed/22101114>

415. Hoskin, P.J., *et al.* Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. *J Clin Oncol*, 2010. 28: 4912.
<https://www.ncbi.nlm.nih.gov/pubmed/20956620>
416. Kaufman, D.S., *et al.* Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology*, 2009. 73: 833.
<https://www.ncbi.nlm.nih.gov/pubmed/19100600>
417. De Santis, M., *et al.* Combined chemoradiotherapy with gemcitabine in patients with locally advanced inoperable transitional cell carcinoma of the urinary bladder and/or in patients ineligible for surgery: a phase I trial. *Ann Oncol*, 2014. 25: 1789.
<https://www.ncbi.nlm.nih.gov/pubmed/24936582>
418. Mak, R.H., *et al.* Bladder preservation: optimizing radiotherapy and integrated treatment strategies. *BJU Int*, 2008. 102: 1345.
<https://www.ncbi.nlm.nih.gov/pubmed/19035903>
419. Huddart, R.A., *et al.* Randomized Noninferiority Trial of Reduced High-Dose Volume Versus Standard Volume Radiation Therapy for Muscle-Invasive Bladder Cancer: Results of the BC2001 Trial (CRUK/01/004). *Int J Radiat Oncol Biol Phys*, 2013. 87: 261.
<https://www.ncbi.nlm.nih.gov/pubmed/23958147>
420. Ramani, V.A., *et al.* Differential complication rates following radical cystectomy in the irradiated and nonirradiated pelvis. *Eur Urol*, 2010. 57: 1058.
<https://www.ncbi.nlm.nih.gov/pubmed/20022162>
421. Cohen, S.M., *et al.* The role of perioperative chemotherapy in the treatment of urothelial cancer. *Oncologist*, 2006. 11: 630.
<https://www.ncbi.nlm.nih.gov/pubmed/16794242>
422. James, N., *et al.*, Bladder Cancer, in Perez and Brady's Principles and Practice of Radiation Oncology, E. Halperin, D. Wazer, C. Perez & L. Brady, Eds. 2012, Lippincott Williams & Wilkins: Philadelphia.
423. Mitin, T., *et al.* Long-Term Outcomes Among Patients Who Achieve Complete or Near-Complete Responses After the Induction Phase of Bladder-Preserving Combined-Modality Therapy for Muscle-Invasive Bladder Cancer: A Pooled Analysis of NRG Oncology/RTOG 9906 and 0233. *Int J Radiat Oncol Biol Phys*, 2016. 94: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/26700703>
424. Sylvester, R., *et al.* The role of adjuvant combination chemotherapy after cystectomy in locally advanced bladder cancer: what we do not know and why. *Ann Oncol*, 2000. 11: 851.
<https://www.ncbi.nlm.nih.gov/pubmed/10997813>
425. Donat, S.M., *et al.* Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. *Eur Urol*, 2009. 55: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/18640770>
426. ABC Meta-analysis Coll. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol*, 2005. 48: 189.
<https://www.ncbi.nlm.nih.gov/pubmed/15939530>
427. Leow, J.J., *et al.* Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol*, 2014. 66: 42.
<https://www.ncbi.nlm.nih.gov/pubmed/24018020>
428. Cognetti, F., *et al.* Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Ann Oncol*, 2012. 23: 695.
<https://www.ncbi.nlm.nih.gov/pubmed/21859900>
429. Paz-Ares, L.G., *et al.* Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: Results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study. *J Clin Oncol*, 2010. vol. 28 no. 18_suppl.
http://meeting.ascopubs.org/cgi/content/abstract/28/18_suppl/LBA4518
430. Stadler, W.M., *et al.* Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. *J Clin Oncol*, 2011. 29: 3443.
<https://www.ncbi.nlm.nih.gov/pubmed/21810677>

431. Lehmann, J., *et al.* Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. *BJU Int*, 2006. 97: 42.
<https://www.ncbi.nlm.nih.gov/pubmed/16336326>
432. Freiha, F., *et al.* A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol*, 1996. 155: 495.
<https://www.ncbi.nlm.nih.gov/pubmed/8558644>
433. Stockle, M., *et al.* Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. *J Urol*, 1995. 153: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/7966789>
434. Studer, U.E., *et al.* Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. *J Urol*, 1994. 152: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/8201695>
435. Skinner, D.G., *et al.* Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. *Semin Urol*, 1990. 8: 279.
<https://www.ncbi.nlm.nih.gov/pubmed/2284533>
436. Lehmann, J., *et al.* Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: results of a randomized, multicenter, phase III trial (AUO-AB 05/95). *J Clin Oncol*, 2005. 23: 4963.
<https://www.ncbi.nlm.nih.gov/pubmed/15939920>
437. Svatek, R.S., *et al.* The effectiveness of off-protocol adjuvant chemotherapy for patients with urothelial carcinoma of the urinary bladder. *Clin Cancer Res*, 2010. 16: 4461.
<https://www.ncbi.nlm.nih.gov/pubmed/20651056>
438. Sternberg, C.N., *et al.* Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol*, 2015. 16: 76.
<https://www.ncbi.nlm.nih.gov/pubmed/25498218>
439. von der Maase, H., *et al.* Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol*, 2005. 23: 4602.
<https://www.ncbi.nlm.nih.gov/pubmed/17383078>
440. Sternberg, C.N. Perioperative chemotherapy in muscle-invasive bladder cancer to enhance survival and/or as a strategy for bladder preservation. *Semin Oncol*, 2007. 34: 122.
<https://www.ncbi.nlm.nih.gov/pubmed/17382795>
441. Rosenberg, J.E., *et al.* Update on chemotherapy for advanced bladder cancer. *J Urol*, 2005. 174: 14.
<https://www.ncbi.nlm.nih.gov/pubmed/15947569>
442. Sternberg, C.N., *et al.* Gemcitabine, paclitaxel, pemetrexed and other newer agents in urothelial and kidney cancers. *Crit Rev Oncol Hematol*, 2003. 46 Suppl: S105.
<https://www.ncbi.nlm.nih.gov/pubmed/12850531>
443. Bellmunt, J., *et al.* Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. *Cancer*, 2002. 95: 751.
<https://www.ncbi.nlm.nih.gov/pubmed/12209718>
444. Sengelov, L., *et al.* Metastatic urothelial cancer: evaluation of prognostic factors and change in prognosis during the last twenty years. *Eur Urol*, 2001. 39: 634.
<https://www.ncbi.nlm.nih.gov/pubmed/11464051>
445. De Santis, M., *et al.* Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol*, 2012. 30: 191.
<https://www.ncbi.nlm.nih.gov/pubmed/22162575>
446. Bellmunt, J., *et al.* Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol*, 2010. 28: 1850.
<https://www.ncbi.nlm.nih.gov/pubmed/20231682>
447. Carles, J., *et al.* Feasibility study of gemcitabine and cisplatin administered every two weeks in patients with advanced urothelial tumors and impaired renal function. *Clin Transl Oncol*, 2006. 8: 755.
<https://www.ncbi.nlm.nih.gov/pubmed/17074675>

448. Hussain, S.A., *et al.* A study of split-dose cisplatin-based neo-adjuvant chemotherapy in muscle-invasive bladder cancer. *Oncol Lett*, 2012. 3: 855.
<https://www.ncbi.nlm.nih.gov/pubmed/22741006>
449. Hussain, S.A., *et al.* A phase I/II study of gemcitabine and fractionated cisplatin in an outpatient setting using a 21-day schedule in patients with advanced and metastatic bladder cancer. *Br J Cancer*, 2004. 91: 844.
<https://www.ncbi.nlm.nih.gov/pubmed/15292922>
450. Morales-Barrera, R., *et al.* Cisplatin and gemcitabine administered every two weeks in patients with locally advanced or metastatic urothelial carcinoma and impaired renal function. *Eur J Cancer*, 2012. 48: 1816.
<https://www.ncbi.nlm.nih.gov/pubmed/22595043>
451. Bamias, A., *et al.* Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). *Ann Oncol*, 2013. 24: 1011.
<https://www.ncbi.nlm.nih.gov/pubmed/23136231>
452. Galsky, M.D., *et al.* Cisplatin-based combination chemotherapy in septuagenarians with metastatic urothelial cancer. *Urol Oncol*, 2014. 32: 30.e15.
<https://www.ncbi.nlm.nih.gov/pubmed/23428534>
453. De Santis, M., *et al.* Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer “unfit” for cisplatin-based chemotherapy: phase II--results of EORTC study 30986. *J Clin Oncol*, 2009. 27: 5634.
<https://www.ncbi.nlm.nih.gov/pubmed/19786668>
454. Galsky, M.D., *et al.* A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol*, 2011. 12: 211.
<https://www.ncbi.nlm.nih.gov/pubmed/21376284>
455. Galsky, M.D., *et al.* Treatment of patients with metastatic urothelial cancer “unfit” for Cisplatin-based chemotherapy. *J Clin Oncol*, 2011. 29: 2432.
<https://www.ncbi.nlm.nih.gov/pubmed/21555688>
456. Dash, A., *et al.* Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer*, 2006. 107: 506.
<https://www.ncbi.nlm.nih.gov/pubmed/16773629>
457. Nogue-Aliguer, M., *et al.* Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. *Cancer*, 2003. 97: 2180.
<https://www.ncbi.nlm.nih.gov/pubmed/12712469>
458. Balducci, L., *et al.* Management of cancer in the older person: a practical approach. *Oncologist*, 2000. 5: 224.
<https://www.ncbi.nlm.nih.gov/pubmed/10884501>
459. De Santis, M., *et al.* New developments in first- and second-line chemotherapy for transitional cell, squamous cell and adenocarcinoma of the bladder. *Curr Opin Urol*, 2007. 17: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/17762632>
460. Raj, G.V., *et al.* Formulas calculating creatinine clearance are inadequate for determining eligibility for Cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol*, 2006. 24: 3095.
<https://www.ncbi.nlm.nih.gov/pubmed/16809735>
461. von der Maase, H. Gemcitabine in transitional cell carcinoma of the urothelium. *Expert Rev Anticancer Ther*, 2003. 3: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/12597345>
462. Yafi, F.A., *et al.* First- and second-line therapy for metastatic urothelial carcinoma of the bladder. *Curr Oncol*, 2011. 18: e25.
<https://www.ncbi.nlm.nih.gov/pubmed/21331269>
463. Bellmunt, J., *et al.* New therapeutic challenges in advanced bladder cancer. *Semin Oncol*, 2012. 39: 598.
<https://www.ncbi.nlm.nih.gov/pubmed/23040256>
464. Gabilove, J.L., *et al.* Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med*, 1988. 318: 1414.
<https://www.ncbi.nlm.nih.gov/pubmed/2452983>
465. Bamias, A., *et al.* Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. *J Clin Oncol*, 2004. 22: 220.
<https://www.ncbi.nlm.nih.gov/pubmed/14665607>

466. Sternberg, C.N., *et al.* Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol*, 2001. 19: 2638.
<https://www.ncbi.nlm.nih.gov/pubmed/11352955>
467. Sternberg, C.N., *et al.* Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer*, 2006. 42: 50.
<https://www.ncbi.nlm.nih.gov/pubmed/16330205>
468. Bellmunt, J., *et al.* Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. *J Clin Oncol*, 2012. 30: 1107.
<https://www.ncbi.nlm.nih.gov/pubmed/22370319>
469. Galsky, M.D., *et al.* Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. *Ann Oncol*, 2012. 23: 406.
<https://www.ncbi.nlm.nih.gov/pubmed/21543626>
470. Albers, P., *et al.* Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma - prognostic factors for response and improvement of quality of life. *Onkologie*, 2002. 25: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/11893883>
471. Sternberg, C.N., *et al.* Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer*, 2001. 92: 2993.
<https://www.ncbi.nlm.nih.gov/pubmed/11753976>
472. Meluch, A.A., *et al.* Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie pearl cancer research network. *J Clin Oncol*, 2001. 19: 3018.
<https://www.ncbi.nlm.nih.gov/pubmed/11408496>
473. Parameswaran R, *et al.* A Hoosier Oncology Group phase II study of weekly paclitaxel and gemcitabine in advanced transitional cell (TCC) carcinoma of the bladder. *Proc Am Soc Clin Oncol*, 2001. 200. [No abstract available].
474. Guardino AE, Gemcitabine and paclitaxel as second line chemotherapy for advanced urothelial malignancies. *Proc Am Soc Clin Oncol* 2002. 21. [No abstract available].
475. Fechner, G., *et al.* Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). *Int J Clin Pract*, 2006. 60: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/16409425>
476. Kaufman DS, *et al.* Gemcitabine (G) and paclitaxel (P) every two weeks (GP2w): a completed multicenter phase II trial in locally advanced or metastatic urothelial cancer (UC). *Proc Am Soc Clin Oncol* 2002. 21. [No abstract available].
477. Calabro, F., *et al.* Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. *Cancer*, 2009. 115: 2652.
<https://www.ncbi.nlm.nih.gov/pubmed/19396817>
478. Ko, Y.J., *et al.* Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study. *Lancet Oncol*, 2013. 14: 769.
<https://www.ncbi.nlm.nih.gov/pubmed/23706985>
479. Oing, C., *et al.* Second Line Chemotherapy for Advanced and Metastatic Urothelial Carcinoma: Vinflunine and Beyond-A Comprehensive Review of the Current Literature. *J Urol*, 2016. 195: 254.
<https://www.ncbi.nlm.nih.gov/pubmed/26410730>
480. Raggi, D., *et al.* Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. *Ann Oncol*, 2016. 27: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/26487582>
481. Albers, P., *et al.* Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. *Ann Oncol*, 2011. 22: 288.
<https://www.ncbi.nlm.nih.gov/pubmed/20682548>
482. Culine, S., *et al.* A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Br J Cancer*, 2006. 94: 1395.
<https://www.ncbi.nlm.nih.gov/pubmed/16622447>

483. Bellmunt, J., *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol*, 2009. 27: 4454.
<https://www.ncbi.nlm.nih.gov/pubmed/19687335>
484. Stadler, W.M. Gemcitabine doublets in advanced urothelial cancer. *Semin Oncol*, 2002. 29: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/11894003>
485. Hussain, M., *et al.* Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. *J Clin Oncol*, 2001. 19: 2527.
<https://www.ncbi.nlm.nih.gov/pubmed/11331332>
486. Abe, T., *et al.* Impact of multimodal treatment on survival in patients with metastatic urothelial cancer. *Eur Urol*, 2007. 52: 1106.
<https://www.ncbi.nlm.nih.gov/pubmed/17367917>
487. Bekku, K., *et al.* Could salvage surgery after chemotherapy have clinical impact on cancer survival of patients with metastatic urothelial carcinoma? *Int J Clin Oncol*, 2013. 18: 110.
<https://www.ncbi.nlm.nih.gov/pubmed/22095246>
488. Cowles, R.S., *et al.* Long-term results following thoracotomy for metastatic bladder cancer. *Urology*, 1982. 20: 390.
<https://www.ncbi.nlm.nih.gov/pubmed/7147508>
489. de Vries, R.R., *et al.* Long-term survival after combined modality treatment in metastatic bladder cancer patients presenting with supra-regional tumor positive lymph nodes only. *Eur J Surg Oncol*, 2009. 35: 352.
<https://www.ncbi.nlm.nih.gov/pubmed/18722076>
490. Dodd, P.M., *et al.* Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. *J Clin Oncol*, 1999. 17: 2546.
<https://www.ncbi.nlm.nih.gov/pubmed/10561321>
491. Donat, S.M., *et al.* Methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy and cystectomy for unresectable bladder cancer. *J Urol*, 1996. 156: 368.
<https://www.ncbi.nlm.nih.gov/pubmed/8683681>
492. Gowardhan, B., *et al.* Twenty-three years of disease-free survival following cutaneous metastasis from a primary bladder transitional cell carcinoma. *Int J Urol*, 2004. 11: 1031.
<https://www.ncbi.nlm.nih.gov/pubmed/15509212>
493. Kanzaki, R., *et al.* Outcome of surgical resection of pulmonary metastasis from urinary tract transitional cell carcinoma. *Interact Cardiovasc Thorac Surg*, 2010. 11: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/20395251>
494. Ku, J.H., *et al.* Metastasis of transitional cell carcinoma to the lower abdominal wall 20 years after cystectomy. *Yonsei Med J*, 2005. 46: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/15744826>
495. Lehmann, J., *et al.* Surgery for metastatic urothelial carcinoma with curative intent: the German experience (AUO AB 30/05). *Eur Urol*, 2009. 55: 1293.
<https://www.ncbi.nlm.nih.gov/pubmed/19058907>
496. Matsuguma, H., *et al.* Is there a role for pulmonary metastasectomy with a curative intent in patients with metastatic urinary transitional cell carcinoma? *Ann Thorac Surg*, 2011. 92: 449.
<https://www.ncbi.nlm.nih.gov/pubmed/21801905>
497. Miller, R.S., *et al.* Cisplatin, methotrexate and vinblastine plus surgical restaging for patients with advanced transitional cell carcinoma of the urothelium. *J Urol*, 1993. 150: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/8510277>
498. Otto, T., *et al.* Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. *Urology*, 2001. 57: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/11164143>
499. Sarmiento, J.M., *et al.* Solitary cerebral metastasis from transitional cell carcinoma after a 14-year remission of urinary bladder cancer treated with gemcitabine: Case report and literature review. *Surg Neurol Int*, 2012. 3: 82.
<https://www.ncbi.nlm.nih.gov/pubmed/22937482>
500. Tanis, P.J., *et al.* Surgery for isolated lung metastasis in two patients with bladder cancer. *Urology*, 2005. 66: 881.
<https://www.ncbi.nlm.nih.gov/pubmed/16230169>
501. Sweeney, P., *et al.* Is there a therapeutic role for post-chemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma of the bladder? *J Urol*, 2003. 169: 2113.
<https://www.ncbi.nlm.nih.gov/pubmed/12771730>

502. Siefker-Radtke, A.O., *et al.* Is there a role for surgery in the management of metastatic urothelial cancer? The M. D. Anderson experience. *J Urol*, 2004. 171: 145.
<https://www.ncbi.nlm.nih.gov/pubmed/14665863>
503. Coleman, R.E. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev*, 2001. 27: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/11417967>
504. Aapro, M., *et al.* Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol*, 2008. 19: 420.
<https://www.ncbi.nlm.nih.gov/pubmed/17906299>
505. Zaghoul, M.S., *et al.* A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer. *Int J Clin Oncol*, 2010. 15: 382.
<https://www.ncbi.nlm.nih.gov/pubmed/20354750>
506. Henry, D.H., *et al.* Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol*, 2011. 29: 1125.
<https://www.ncbi.nlm.nih.gov/pubmed/21343556>
507. Rosen, L.S., *et al.* Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer*, 2004. 100: 2613.
<https://www.ncbi.nlm.nih.gov/pubmed/15197804>
508. Powles, T., *et al.* MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature*, 2014. 515: 558.
<https://www.ncbi.nlm.nih.gov/pubmed/25428503>
509. Rosenberg, J.E., *et al.* Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*, 2016. 387: 1909.
<https://www.ncbi.nlm.nih.gov/pubmed/26952546>
510. Youssef, R.F., *et al.* Molecular targets and targeted therapies in bladder cancer management. *World J Urol*, 2009. 27: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/19039591>
511. Shariat, S.F., *et al.* Association of angiogenesis related markers with bladder cancer outcomes and other molecular markers. *J Urol*, 2010. 183: 1744.
<https://www.ncbi.nlm.nih.gov/pubmed/20299037>
512. Song, S., *et al.* Fibroblast growth factors: an epigenetic mechanism of broad spectrum resistance to anticancer drugs. *Proc Natl Acad Sci USA*, 2000. 97: 8658.
<https://www.ncbi.nlm.nih.gov/pubmed/10890892>
513. Gomez-Roman, J.J., *et al.* Fibroblast growth factor receptor 3 is overexpressed in urinary tract carcinomas and modulates the neoplastic cell growth. *Clin Cancer Res*, 2005. 11: 459.
<https://www.ncbi.nlm.nih.gov/pubmed/15701828>
514. Ioachim, E., *et al.* Thrombospondin-1 expression in urothelial carcinoma: prognostic significance and association with p53 alterations, tumour angiogenesis and extracellular matrix components. *BMC Cancer*, 2006. 6: 140.
<https://www.ncbi.nlm.nih.gov/pubmed/16732887>
515. Gallagher, D.J., *et al.* Detection of circulating tumor cells in patients with urothelial cancer. *Ann Oncol*, 2009. 20: 305.
<https://www.ncbi.nlm.nih.gov/pubmed/18836088>
516. Flaig, T.W., *et al.* Detection of circulating tumor cells in metastatic and clinically localized urothelial carcinoma. *Urology*, 2011. 78: 863.
<https://www.ncbi.nlm.nih.gov/pubmed/21813167>
517. Hoffmann, A.C., *et al.* MDR1 and ERCC1 expression predict outcome of patients with locally advanced bladder cancer receiving adjuvant chemotherapy. *Neoplasia*, 2010. 12: 628.
<https://www.ncbi.nlm.nih.gov/pubmed/20689757>
518. Cella, D.F., *et al.* The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*, 1993. 11: 570.
<https://www.ncbi.nlm.nih.gov/pubmed/8445433>
519. Aaronson, N.K., *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*, 1993. 85: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/8433390>

520. Sogni, F., *et al.* Morbidity and quality of life in elderly patients receiving ileal conduit or orthotopic neobladder after radical cystectomy for invasive bladder cancer. *Urology*, 2008. 71: 919.
<https://www.ncbi.nlm.nih.gov/pubmed/18355900>
521. Ware, J.E. Jr., *et al.* The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*, 1992. 30: 473.
<https://www.ncbi.nlm.nih.gov/pubmed/1593914>
522. Ware, J.E. Jr., *et al.* Evaluating translations of health status questionnaires. Methods from the IQOLA project. *International Quality of Life Assessment. Int J Technol Assess Health Care*, 1995. 11: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/7591551>
523. Gilbert, S.M., *et al.* Development and validation of the Bladder Cancer Index: a comprehensive, disease specific measure of health related quality of life in patients with localized bladder cancer. *J Urol*, 2010. 183: 1764.
<https://www.ncbi.nlm.nih.gov/pubmed/20299056>
524. Ramirez, A., *et al.* Exploration of health-related quality of life areas that may distinguish between continent diversion and ileal conduit patients. *Can J Urol*, 2005. 12: 2537.
<https://www.ncbi.nlm.nih.gov/pubmed/15777491>
525. Saika, T., *et al.* Health-related quality of life after radical cystectomy for bladder cancer in elderly patients with an ileal conduit, ureterocutaneostomy, or orthotopic urinary reservoir: a comparative questionnaire survey. *Acta Med Okayama*, 2007. 61: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/17853939>
526. Cerruto, M.A., *et al.* Systematic review and meta-analysis of non RCT's on health related quality of life after radical cystectomy using validated questionnaires: Better results with orthotopic neobladder versus ileal conduit. *Eur J Surg Oncol*, 2016. 42: 343.
<https://www.ncbi.nlm.nih.gov/pubmed/26620844>
527. Singh, V., *et al.* Prospective comparison of quality-of-life outcomes between ileal conduit urinary diversion and orthotopic neobladder reconstruction after radical cystectomy: a statistical model. *BJU Int*, 2014. 113: 726.
<https://www.ncbi.nlm.nih.gov/pubmed/24053658>
528. Roychowdhury, D.F., *et al.* Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. *J Clin Oncol*, 2003. 21: 673.
<https://www.ncbi.nlm.nih.gov/pubmed/12586805>
529. Hedgepeth, R.C., *et al.* Body image and bladder cancer specific quality of life in patients with ileal conduit and neobladder urinary diversions. *Urology*, 2010. 76: 671.
<https://www.ncbi.nlm.nih.gov/pubmed/20451964>
530. Bartsch, G., *et al.* Urinary functional outcomes in female neobladder patients. *World J Urol*, 2014. 32: 221.
<https://www.ncbi.nlm.nih.gov/pubmed/24317553>
531. Fossa, S.D., *et al.* Quality of life in patients with muscle-infiltrating bladder cancer and hormone-resistant prostatic cancer. *Eur Urol*, 1989. 16: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/2476317>
532. Mommsen, S., *et al.* Quality of life in patients with advanced bladder cancer. A randomized study comparing cystectomy and irradiation--the Danish Bladder Cancer Study Group (DAVECA protocol 8201). *Scand J Urol Nephrol Suppl*, 1989. 125: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/2699072>
533. Fokdal, L., *et al.* Radical radiotherapy for urinary bladder cancer: treatment outcomes. *Expert Rev Anticancer Ther*, 2006. 6: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/16445379>
534. Rodel, C., *et al.* Organ preservation by combined modality treatment in bladder cancer: the European perspective. *Semin Radiat Oncol*, 2005. 15: 28.
<https://www.ncbi.nlm.nih.gov/pubmed/15662604>
535. Lodde, M., *et al.* Four years experience in bladder preserving management for muscle invasive bladder cancer. *Eur Urol*, 2005. 47: 773.
<https://www.ncbi.nlm.nih.gov/pubmed/15925072>
536. Rodel, C., *et al.* Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol*, 2002. 20: 3061.
<https://www.ncbi.nlm.nih.gov/pubmed/12118019>
537. Merseburger, A.S., *et al.* The value of bladder-conserving strategies in muscle-invasive bladder carcinoma compared with radical surgery. *Curr Opin Urol*, 2007. 17: 358.
<https://www.ncbi.nlm.nih.gov/pubmed/17762631>

538. Rodel, C., *et al.* Trimodality treatment and selective organ preservation for bladder cancer. *J Clin Oncol*, 2006. 24: 5536.
<https://www.ncbi.nlm.nih.gov/pubmed/17158539>
539. Malkowicz, S.B., *et al.* Muscle-invasive urothelial carcinoma of the bladder. *Urology*, 2007. 69: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/17280906>
540. Karakiewicz, P.I., *et al.* Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol*, 2006. 176: 1354.
<https://www.ncbi.nlm.nih.gov/pubmed/16952631>
541. Zaak, D., *et al.* Predicting individual outcomes after radical cystectomy: an external validation of current nomograms. *BJU Int*, 2010. 106: 342.
<https://www.ncbi.nlm.nih.gov/pubmed/20002664>
542. Giannarini, G., *et al.* Do patients benefit from routine follow-up to detect recurrences after radical cystectomy and ileal orthotopic bladder substitution? *Eur Urol*, 2010. 58: 486.
<https://www.ncbi.nlm.nih.gov/pubmed/20541311>
543. Volkmer, B.G., *et al.* Oncological followup after radical cystectomy for bladder cancer-is there any benefit? *J Urol*, 2009. 181: 1587.
<https://www.ncbi.nlm.nih.gov/pubmed/19233433>
544. Soukup, V., *et al.* Follow-up after surgical treatment of bladder cancer: a critical analysis of the literature. *Eur Urol*, 2012. 62: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/22609313>
545. Huguet, J. Follow-up after radical cystectomy based on patterns of tumour recurrence and its risk factors. *Actas Urol Esp*, 2013. 37: 376.
<https://www.ncbi.nlm.nih.gov/pubmed/23611464>
546. Ghoneim, M.A., *et al.* Radical cystectomy for carcinoma of the bladder: 2,720 consecutive cases 5 years later. *J Urol*, 2008. 180: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/18485392>
547. Donat, S.M. Staged based directed surveillance of invasive bladder cancer following radical cystectomy: valuable and effective? *World J Urol*, 2006. 24: 557.
<https://www.ncbi.nlm.nih.gov/pubmed/17009050>
548. Mathers, M.J., *et al.* Is there evidence for a multidisciplinary follow-up after urological cancer? An evaluation of subsequent cancers. *World J Urol*, 2008. 26: 251.
<https://www.ncbi.nlm.nih.gov/pubmed/18421461>
549. Vrooman, O.P., *et al.* Follow-up of patients after curative bladder cancer treatment: guidelines vs. practice. *Curr Opin Urol*, 2010. 20: 437.
<https://www.ncbi.nlm.nih.gov/pubmed/20657286>
550. Cagiannos, I., *et al.* Surveillance strategies after definitive therapy of invasive bladder cancer. *Can Urol Assoc J*, 2009. 3: S237.
<https://www.ncbi.nlm.nih.gov/pubmed/20019993>
551. Freeman, J.A., *et al.* Urethral recurrence in patients with orthotopic ileal neobladders. *J Urol*, 1996. 156: 1615.
<https://www.ncbi.nlm.nih.gov/pubmed/8863551>
552. Huguet, J., *et al.* Management of urethral recurrence in patients with Studer ileal neobladder. *Eur Urol*, 2003. 43: 495.
<https://www.ncbi.nlm.nih.gov/pubmed/12705993>
553. Nieder, A.M., *et al.* Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. *Urology*, 2004. 64: 950.
<https://www.ncbi.nlm.nih.gov/pubmed/15533484>
554. Varol, C., *et al.* Treatment of urethral recurrence following radical cystectomy and ileal bladder substitution. *J Urol*, 2004. 172: 937.
<https://www.ncbi.nlm.nih.gov/pubmed/15311003>
555. Lin, D.W., *et al.* Value of urethral wash cytology in the retained male urethra after radical cystoprostatectomy. *J Urol*, 2003. 169: 961.
<https://www.ncbi.nlm.nih.gov/pubmed/12576822>
556. Sherwood, J.B., *et al.* The diagnosis and treatment of urethral recurrence after radical cystectomy. *Urol Oncol*, 2006. 24: 356.
<https://www.ncbi.nlm.nih.gov/pubmed/16818191>
557. Clark, P.E., *et al.* The management of urethral transitional cell carcinoma after radical cystectomy for invasive bladder cancer. *J Urol*, 2004. 172: 1342.
<https://www.ncbi.nlm.nih.gov/pubmed/15371837>

558. Bochner, B.H., *et al.* Follow-up strategies and management of recurrence in urologic oncology bladder cancer: invasive bladder cancer. *Urol Clin North Am*, 2003. 30: 777.
<https://www.ncbi.nlm.nih.gov/pubmed/14680314>
559. Picozzi, S., *et al.* Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *J Urol*, 2012. 188: 2046.
<https://www.ncbi.nlm.nih.gov/pubmed/23083867>
560. Sanderson, K.M., *et al.* Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year followup. *J Urol*, 2007. 177: 2088.
<https://www.ncbi.nlm.nih.gov/pubmed/17509294>
561. Gupta, A., *et al.* Risk of fracture after radical cystectomy and urinary diversion for bladder cancer. *J Clin Oncol*, 2014. 32: 3291.
<https://www.ncbi.nlm.nih.gov/pubmed/25185104>

10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines Working Group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=panel>.

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EAU Guidelines on Primary Urethral Carcinoma

G. Gakis, J.A. Witjes, E. Compérat, N.C. Cowan, V. Hernández,
T. Le Bret, A. Lorch, M.J. Ribal, A.G. van der Heijden
Guidelines Associates: M. Bruins, E. Linares Espinós,
M. Rouanne, Y. Neuzillet, E. Veskimäe

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1. INTRODUCTION

1.1 Aims and scope

The aim of these guidelines is to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma (UC). When the first carcinoma in the urinary tract is detected in the urethra, this is defined as primary UC, in contrast to secondary UC, which presents as recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary UC is reported after radical cystectomy for bladder cancer [1, 2] (see Chapter 7.4 of the EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer (MIBC) [2]).

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on MIBC is responsible for this publication. This is an international multidisciplinary group of clinicians, including urologists, a pathologist, an oncologist and a radiologist. Members of this panel have been selected based on their expertise to represent the professionals treating patients suspected of suffering from urethral carcinoma. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website Uroweb: www.uroweb.org/guidelines/primary-urethral-carcinoma/.

1.3 Publication history and summary of changes

The Primary Urethral Carcinoma Guidelines were first published in 2013 [3]. This is the third update of this document.

1.3.1 Summary of changes

The literature for the complete document has been assessed and updated, where relevant.

2. METHODS

2.1 Data identification

For the 2017 Primary urethral Carcinoma Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. An updated systematic literature search was performed to identify studies reporting data on urethral malignancies since the prior search, covering a time frame between January 1st 2014 and September 20th, 2016. Databases searched included Ovid (Medline), EMBASE and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. A total of 309 records were identified, retrieved and screened for relevance. A detailed search strategy is available online:

<https://uroweb.org/guideline/primary-urethral-carcinoma/?type=appendices-publications>.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>.

A list of Associations endorsing the EAU Guidelines can also be viewed on line at the above address.

2.2 Review

This document was peer-reviewed prior to publication in 2015.

2.3 Future goals

The MIBC Guidelines Panel aims to systematically address the following key clinical topics for future updates of the Primary Urethral Carcinoma Guidelines:

- assessment of the accuracy of radiological imaging (MRI) for local staging of primary UC and its predictive value on clinical decision-making;
- the (long-term) efficacy of urethral-sparing surgery and radiochemotherapy for genital preservation in localised tumours;
- the prognostic impact of neoadjuvant and adjuvant treatment modalities in locally advanced disease.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Primary UC is considered a rare cancer, accounting for < 1% of all malignancies [5] (ICD-O3 topography code: C68.0 [6]). In early 2008, the prevalence of UC in the 27 European Union countries was 4,292 cases with an estimated annual incidence of 655 new cases [7]. The age-standardised ratio was 1.1 per million inhabitants (1.6/million in men and 0.6/million in women; with a male to female ratio of 2.9) [7]. There were differences between European regions; potentially caused by registration or classification [7]. Likewise, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the incidence of primary UC peaked in the > 75 years age group (7.6/million). The age-standardised rate was 4.3/million in men and 1.5/million in women, and was almost negligible in those aged < 55 years (0.2/million) [8].

3.2 Aetiology

For male primary UC, various predisposing factors have been reported, including urethral strictures [9, 10], chronic irritation after intermittent catheterisation/urethroplasty [11-13], external beam irradiation therapy [14], radioactive seed implantation [15], and chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e. condylomata associated with human papilloma virus 16) [16, 17]. In female UC, urethral diverticula [18-20] and recurrent urinary tract infections [21] have been associated with primary UC. Clear cell adenocarcinoma (AC) may also have a congenital origin [22, 23].

3.3 Histopathology

Both the Surveillance of Rare Cancers in Europe (RARECARE) project and SEER database have reported that urothelial carcinoma of the urethra is the predominant histological type of primary urethral cancer (54-65%), followed by squamous cell carcinoma (SCC) (16-22%) and AC (10-16%) [7, 8]. A recent SEER analysis of 2,065 men with primary UC (mean age: 73 years) found that UC was most common (78%), and SCC (12%) and AC (5%) were significantly less frequent [24]. In women, a recent report of the Dutch National Cancer Registry on primary urethral cancer reported that UC occurred in 45% of cases, followed by AC in 29%, SCC in 19%, and other histological entities in 6% [25].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Tumour, Node, Metastasis (TNM) staging system

In men and women, UC is classified according to the 8th edition of the TNM classification [6] (Table 4.1). It should be noted that there is a separate TNM staging system for prostatic UC [6]. Of note, for cancers occurring in the urethral diverticulum, stage T2 is not applicable as urethral diverticula are lacking periurethral muscle [26].

Table 4.1: TNM classification (8th edition) for urethral carcinoma (UC) [6]
Primary tumour stage is separated into UC and UC of the prostate

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Urethra (male and female)	
Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma <i>in situ</i>
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following structures: corpus spongiosum, prostate, periurethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder)
Urothelial (transitional cell) carcinoma of the prostate	
Tis pu	Carcinoma <i>in situ</i> , involvement of prostatic urethra
Tis pd	Carcinoma <i>in situ</i> , involvement of prostatic ducts
T1	Tumour invades subepithelial connective tissue (for tumours involving prostatic urethra only)
T2	Tumour invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder or rectum)
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node
N2	Metastasis in multiple lymph nodes
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.2 Tumour grade

The former World Health Organization (WHO) grading system of 1973 which differentiated urothelial carcinomas into three different grades (G1-G3) has been replaced by the grading system of 2004 that differentiates urothelial UC into papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade and high grade. Non-urothelial UC is graded by a trinomial system that differentiates between well-differentiated (G1), moderately-differentiated (G2), and poorly-differentiated tumours (G3). Table 4.2 lists the different grading systems according to the WHO 1973 and 2004 systems [27]. The 2004 classification corresponds to the new 2016 WHO classification [28].

Table 4.2: Histopathological grading of urothelial and non-urothelial primary urethral carcinoma [27]

PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated

Non-urothelial urethral carcinoma	
Gx	Tumour grade not assessable
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Recommendation	LE	GR
Use the 2017 TNM classification and 2004/2016 WHO grading systems for pathological staging and grading of primary urethral carcinoma.	3	B

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 History

When becoming clinically apparent, most patients (45-57%) with primary UC present with symptoms associated with locally advanced disease (T3/T4) [26, 27, 29]. At initial presentation visible haematuria or bloody urethral discharge is reported in up to 62% of the cases. Further symptoms of locally advanced disease include; an extraurethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%) or dyspareunia [29].

5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [30]. In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to exclude the presence of colorectal or gynaecological malignancies. Bilateral inguinal palpation should be conducted to assess the presence of enlarged lymph nodes (LNs), describing location, size and mobility [31].

5.3 Urinary cytology

Cytological assessment of urine specimens in suspect cases of primary UC should be conducted according to the Paris system [32]. The role of urinary cytology in primary UC is limited since its sensitivity ranges between 55% and 59% [33]. Detection rates depend on the underlying histological entity. In male patients, the sensitivity for UC and SCC was reported to be 80% and 50%, respectively, whereas in female patients, sensitivity was found to be 77% for SCC and 50% for UC [32].

5.4 Diagnostic urethrocystoscopy and biopsy

Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location and underlying histology [30]. To enable accurate pathological assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist.

Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [3, 34]. A cold-cup biopsy enables accurate tissue retrieval for histological analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histological diagnosis. In patients with suspected UC of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (between the five and seven o'clock position from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [35].

5.5 Radiological imaging

Radiological imaging of UC aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. For local staging, there is increasing evidence that magnetic resonance imaging (MRI) is an accurate tool for monitoring tumour response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease prior to exenterative surgery [36]. Imaging for regional LN metastases should concentrate on inguinal and pelvic LNs, using either MRI or computed tomography (CT). Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (> cT1N0M0) [36-40]. If imaging of the remainder of the urothelium is required, then CT should include CT urography with an excretory phase [41].

5.6 Regional lymph nodes

Enlarged LNs in UC often represent metastatic disease [42, 43]. In men, lymphatics from the anterior urethra drain into the superficial- and deep inguinal LNs and subsequently to the pelvic (external, obturator and internal iliac) LNs. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic LNs. In women, the lymph of the proximal third drains into the pelvic LN chains, whereas the distal two-thirds initially drain into the superficial- and deep inguinal nodes [44, 45].

Nodal control in UC can be achieved either by regional LN dissection [30], radiotherapy [46] or chemotherapy [42]. Currently, there is still no clear evidence supporting prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with UC. However, in patients with clinically enlarged inguinal/pelvic LNs or invasive tumours, regional lymphadenectomy should be considered as initial treatment since cure might still be achievable with limited disease [30].

Summary of evidence	LE
Patients with clinically enlarged inguinal or pelvic lymph nodes often exhibit pathological lymph node metastasis.	3

Recommendations	LE	GR
Use urethrocytostcopy with biopsy and urinary cytology to diagnose urethral carcinoma.	3	B
Assess the presence of distant metastases by computed tomography of the thorax and abdomen.	3	B
Use pelvic magnetic resonance imaging to assess the local extent of urethral tumour (mapping tumour extension).	3	B

6. PROGNOSIS

6.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the mean one- and five-year overall survival (OS) in patients with UC in Europe is 71% and 54%, respectively [7]. With longer follow-up, a SEER analysis of 1,615 cases reported median five- and ten-year OS rates of 46% and 29%, respectively. Cancer-specific survival (CSS) at five and ten years was 68% and 60%, respectively [8].

6.2 Predictors of survival in primary urethral carcinoma

In Europe, mean five-year OS does not substantially differ between the sexes [7]. Predictors of decreased survival in patients with primary UC are:

- advanced age (> 65 years) and black race [7, 47];
- stage, grade, nodal involvement [43] and metastasis [24];
- tumour size and proximal tumour location [24];
- extent of surgical treatment and treatment modality [24, 47];
- underlying histology [7, 25, 47];
- presence of concomitant bladder cancer [34];
- location of recurrence (urethral vs. non-urethral) [48].

Some limitations have to be taken into account in the interpretation of these results. In the Dutch study, the numbers were low (n = 91) [26]. In the large SEER database (n = 2,046), therapy is not well specified in relation to survival [25]. Finally, in contrast to the RARECARE project [7], the opposite findings were reported in the SEER database in relation to the role of histology on survival in male patients [47].

Summary of evidence	LE
Risk factors for survival in primary urethral carcinoma are: age, race, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and type and modality of treatment.	3

7. DISEASE MANAGEMENT

7.1 Treatment of localised primary urethral carcinoma in males

Previously, treatment of male anterior UC has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin [30]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [49]. Therefore, optimising treatment of distal UC has become the focus of clinicians to improve functional outcome and quality of life, while preserving oncological safety. A retrospective series found no evidence of local recurrence, even with < 5 mm resection margins (median follow-up: 17-37 months), in men with pT1-3N0-2 anterior UC treated with well-defined penis-preserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected LN disease [50]. This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have also been reported in recent series [51, 52].

Summary of evidence	LE
In distal urethral tumours performing a partial urethrectomy with a minimal safety margin does not increase the risk of local recurrence.	3

Recommendation	LE	GR
Offer distal urethrectomy as an alternative to penile amputation in localised anterior urethral tumours, if surgical margins are negative.	3	B

7.2 Treatment of localised urethral carcinoma in females

7.2.1 Urethrectomy and urethra-sparing surgery

In women with localised UC, to provide the highest chance of local cure, primary radical urethrectomy should remove all the periurethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and appendicovesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women [30].

Recent series have reported outcomes in women with mainly anterior UC undergoing primary treatment with urethra-sparing surgery or radiotherapy, compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [53-55]. In long-term series with a median follow-up of 153-175 months, local recurrence rates in women undergoing partial urethrectomy with intra-operative frozen section analysis were 22-60%, and distal sleeve resection of > 2 cm resulted in secondary urinary incontinence in 42% of patients who required additional reconstructive surgery [54].

Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal UC, have also resulted in considerable local failure rates of 16%, with a CSS rate of 50%. This emphasises the critical role of local tumour control in women with distal UC to prevent local and systemic progression [53].

7.2.2 Radiotherapy

In women, radiotherapy was investigated in several older long-term series with a medium follow up of 91-105 months [46, 50]. With a median cumulative dose of 65 Gy (range: 40-106 Gy), the five year local control rate was 64% and seven year CSS was 49% [46]. Most local failures (95%) occurred within the first two years after primary treatment [50]. The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of radiotherapy (external beam radiotherapy [EBRT] vs. interstitial brachytherapy) was not [46]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [56]. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, and cystitis and/or haemorrhage, with 30% of the reported complications graded as severe [46].

Summary of evidence	LE
In anterior tumours, urethra-sparing surgery and local radiotherapy represent alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.	3

Recommendations	LE	GR
Offer urethra-sparing surgery as an alternative to primary urethrectomy to women with anterior urethral tumours, if negative surgical margins can be achieved intra-operatively.	3	B
Offer local radiotherapy as an alternative to urethral surgery to women with localised urethral tumours, but discuss local toxicity.	3	C

7.3 Multimodal treatment in advanced urethral carcinoma in both genders

7.3.1 Preoperative platinum-based chemotherapy

Recent retrospective studies have reported that modern platinum-based polychemotherapeutic regimens are effective in advanced primary UC, providing prolonged survival even in LN-positive disease. Moreover, they have emphasised the critical role of surgery after chemotherapy to achieve long-term survival in patients with locally advanced UC.

In a series of 39 patients treated with perioperative platinum-based chemotherapy for advanced primary UC, preoperative chemotherapy was found to be associated with improved progression-free and OS compared to surgery followed by adjuvant chemotherapy [57]. Another series reported outcomes in 44 patients with advanced primary UC treated with specific cisplatin-based polychemotherapeutic regimens according to the underlying histology. The overall response rate for the various regimens was 72% and the median OS 32 months. Patients who underwent surgery after chemotherapy had a significantly improved OS compared with those who were managed with chemotherapy alone [42].

7.3.2 Preoperative chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra

The clinical feasibility of preoperative local radiotherapy with concurrent radiosensitising chemotherapy as an alternative to surgery in locally advanced SCC has been reported in several recent series. This approach offers a potential for genital preservation [57-62]. The largest and recently updated series reported outcomes in 25 patients with primary locally advanced SCC of the urethra treated with two cycles of 5-fluorouracil and mitomycin C with concurrent EBRT. A complete response to primary chemoradiotherapy was observed in ~80%. The five-year OS and DSS survival was 52% and 68%, respectively. In this updated series, salvage surgery initiated only in non-responders or in case of local failure was not reported to be associated with improved survival [58].

Summary of evidence	LE
In locally advanced urethral carcinoma, cisplatin-based chemotherapy with curative intent prior to surgery improves survival compared to chemotherapy alone, or surgery followed by chemotherapy.	4
In locally advanced squamous cell carcinoma (SCC) of the urethra, the prognostic role and timing of surgery after completion of chemoradiotherapy is unclear.	4

Recommendations	LE	GR
Discuss treatment of patients with locally advanced urethral carcinoma within a multidisciplinary team of urologists, radio-oncologists and oncologists.	4	A
Use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	4	C
In locally advanced SCC of the urethra, offer the combination of curative radiotherapy with radiosensitising chemotherapy for genital preservation.	4	C

7.4 Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent Bacillus-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC [63, 64]. Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs. 66%) [65]. Risk of understaging local extension of prostatic urethral cancer at TUR is increased, especially in patients with ductal or stromal involvement [66]. In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57 and 75% [63, 67]. Some earlier series have reported superior oncological results for the initial use of radical cystoprostatectomy as a primary treatment option in patients with ductal involvement [68, 69]. In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a LN mapping study found that twelve patients had positive LNs, with an increased proportion located above the iliac bifurcation [70].

Summary of evidence	LE
Patients undergoing transurethral resection of the prostate for prostatic urothelial carcinoma (UC) prior to bacillus-Calmette-Guérin (BCG) treatment show superior complete response rates compared to those who do not.	3

Recommendations	LE	GR
Offer a urethra-sparing approach with transurethral resection (TUR) and BCG to patients with non-invasive urethral carcinoma or carcinoma <i>in situ</i> of the prostatic urethra and prostatic ducts.	3	C
In patients with non-invasive UC or carcinoma <i>in situ</i> , perform a prior TUR of the prostate to improve response to BCG.	3	C
In patients not responding to BCG, or in patients with extensive ductal or stromal involvement, perform a cystoprostatectomy with extended pelvic lymphadenectomy.	3	C

8. FOLLOW-UP

Given the low incidence of primary urethral cancer, follow-up has not been investigated systematically so far. Therefore, it seems reasonable to tailor surveillance regimens according to patients' individual risk factors (see Chapter 6.2). In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocystoscopy and cross-sectional imaging despite the lack of specific data.

9. REFERENCES

- Boorjian, S.A., *et al.* Risk factors and outcomes of urethral recurrence following radical cystectomy. *Eur Urol*, 2011. 60: 1266.
<https://www.ncbi.nlm.nih.gov/pubmed/21871713>
- Witjes, J.A., *et al.*, EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Edn. presented at the 32nd EAU Annual Congress London in EAU Guidelines 2017: Arnhem. The Netherlands.
<https://uroweb.org/guideline/primary-urethral-carcinoma/>
- Gakis, G., *et al.* EAU guidelines on primary urethral carcinoma. *Eur Urol*, 2013. 64: 823.
<https://www.ncbi.nlm.nih.gov/pubmed/23582479>
- Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
- Gatta, G., *et al.* Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer*, 2011. 47: 2493.
<https://www.ncbi.nlm.nih.gov/pubmed/22033323>
- Brierley, J.D., *et al.*, TNM classification of malignant tumors. UICC International Union Against Cancer. 2017, Wiley/Blackwell. p. 208.
<http://www.uicc.org/resources/tnm>
- Visser, O., *et al.* Incidence and survival of rare urogenital cancers in Europe. *Eur J Cancer*, 2012. 48: 456.
<https://www.ncbi.nlm.nih.gov/pubmed/22119351>
- Swartz, M.A., *et al.* Incidence of primary urethral carcinoma in the United States. *Urology*, 2006. 68: 1164.
<https://www.ncbi.nlm.nih.gov/pubmed/17141838>
- Medina Perez, M., *et al.* [Squamous carcinoma of the male urethra, its presentation as a scrotal abscess]. *Arch Esp Urol*, 1999. 52: 792.
<https://www.ncbi.nlm.nih.gov/pubmed/10540772>

10. Van de Voorde, W., *et al.* Urethral squamous cell carcinoma associated with urethral stricture and urethroplasty. *Eur J Surg Oncol*, 1994. 20: 478.
<https://www.ncbi.nlm.nih.gov/pubmed/8076714>
11. Colapinto, V., *et al.* Primary carcinoma of the male urethra developing after urethroplasty for stricture. *J Urol*, 1977. 118: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/916053>
12. Mohanty, N.K., *et al.* Squamous cell carcinoma of perineal urethrostomy. *Urol Int*, 1995. 55: 118.
<https://www.ncbi.nlm.nih.gov/pubmed/8533195>
13. Sawczuk, I., *et al.* Post urethroplasty squamous cell carcinoma. *N Y State J Med*, 1986. 86: 261.
<https://www.ncbi.nlm.nih.gov/pubmed/3459083>
14. Mohan, H., *et al.* Squamous cell carcinoma of the prostate. *Int J Urol*, 2003. 10: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/12588611>
15. Arva, N.C., *et al.* Diagnostic dilemmas of squamous differentiation in prostate carcinoma case report and review of the literature. *Diagn Pathol*, 2011. 6: 46.
<https://www.ncbi.nlm.nih.gov/pubmed/21627811>
16. Cupp, M.R., *et al.* Detection of human papillomavirus DNA in primary squamous cell carcinoma of the male urethra. *Urology*, 1996. 48: 551.
<https://www.ncbi.nlm.nih.gov/pubmed/8886059>
17. Wiener, J.S., *et al.* Oncogenic human papillomavirus type 16 is associated with squamous cell cancer of the male urethra. *Cancer Res*, 1992. 52: 5018.
<https://www.ncbi.nlm.nih.gov/pubmed/1325290>
18. Ahmed, K., *et al.* Urethral diverticular carcinoma: an overview of current trends in diagnosis and management. *Int Urol Nephrol*, 2010. 42: 331.
<https://www.ncbi.nlm.nih.gov/pubmed/19649767>
19. Chung, D.E., *et al.* Urethral diverticula in women: discrepancies between magnetic resonance imaging and surgical findings. *J Urol*, 2010. 183: 2265.
<https://www.ncbi.nlm.nih.gov/pubmed/20400161>
20. Thomas, A.A., *et al.* Urethral diverticula in 90 female patients: a study with emphasis on neoplastic alterations. *J Urol*, 2008. 180: 2463.
<https://www.ncbi.nlm.nih.gov/pubmed/18930487>
21. Libby, B., *et al.* Non-surgical treatment of primary female urethral cancer. *Rare Tumors*, 2010. 2: e55.
<https://www.ncbi.nlm.nih.gov/pubmed/21139970>
22. Gandhi, J.S., *et al.* Clear cell adenocarcinoma of the male urethral tract. *Indian J Pathol Microbiol*, 2012. 55: 245.
<https://www.ncbi.nlm.nih.gov/pubmed/22771656>
23. Mehra, R., *et al.* Primary urethral clear-cell adenocarcinoma: comprehensive analysis by surgical pathology, cytopathology, and next-generation sequencing. *Am J Pathol*, 2014. 184: 584.
<https://www.ncbi.nlm.nih.gov/pubmed/24389164>
24. Rabbani, F. Prognostic factors in male urethral cancer. *Cancer*, 2011. 117: 2426.
<https://www.ncbi.nlm.nih.gov/pubmed/24048790>
25. Derksen, J.W., *et al.* Primary urethral carcinoma in females: an epidemiologic study on demographical factors, histological types, tumour stage and survival. *World J Urol*, 2013. 31: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/22614443>
26. Golijanin, D., *et al.* Carcinoma in a bladder diverticulum: presentation and treatment outcome. *J Urol*, 2003. 170: 1761.
<https://www.ncbi.nlm.nih.gov/pubmed/14532771>
27. Eble JN, *et al.* WHO Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs (IARC WHO Classification of Tumours). 2004, Lyon.
<http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb7/BB7.pdf>
28. Comperat, E., *et al.* Immunochemical and molecular assessment of urothelial neoplasms and aspects of the 2016 World Health Organization classification. *Histopathology*, 2016. 69: 717.
<https://www.ncbi.nlm.nih.gov/pubmed/27353436>
29. Gheiler, E.L., *et al.* Management of primary urethral cancer. *Urology*, 1998. 52: 487.
<https://www.ncbi.nlm.nih.gov/pubmed/9730466>
30. Karnes, R.J., *et al.* Surgery for urethral cancer. *Urol Clin North Am*, 2010. 37: 445.
<https://www.ncbi.nlm.nih.gov/pubmed/20674699>
31. Blaivas, J.G., *et al.* Periurethral masses: etiology and diagnosis in a large series of women. *Obstet Gynecol*, 2004. 103: 842.
<https://www.ncbi.nlm.nih.gov/pubmed/15121554>

32. Barkan, G.A., *et al.* The Paris System for Reporting Urinary Cytology: The Quest to Develop a Standardized Terminology. *Acta Cytol*, 2016. 60: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/27318895>
33. Touijer, A.K., *et al.* Role of voided urine cytology in diagnosing primary urethral carcinoma. *Urology*, 2004. 63: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/14751342>
34. Gakis, G., *et al.* Oncological Outcomes of Patients with Concomitant Bladder and Urethral Carcinoma. *Urol Int*, 2016. 97: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/27462702>
35. Donat, S.M., *et al.* The efficacy of transurethral biopsy for predicting the long-term clinical impact of prostatic invasive bladder cancer. *J Urol*, 2001. 165: 1580.
<https://www.ncbi.nlm.nih.gov/pubmed/11342921>
36. Gourtsoyianni, S., *et al.* MRI at the completion of chemoradiotherapy can accurately evaluate the extent of disease in women with advanced urethral carcinoma undergoing anterior pelvic exenteration. *Clin Radiol*, 2011. 66: 1072.
<https://www.ncbi.nlm.nih.gov/pubmed/21839430>
37. Kim, B., *et al.* Imaging of the male urethra. *Semin Ultrasound CT MR*, 2007. 28: 258.
<https://www.ncbi.nlm.nih.gov/pubmed/17874650>
38. Neitlich, J.D., *et al.* Detection of urethral diverticula in women: comparison of a high resolution fast spin echo technique with double balloon urethrography. *J Urol*, 1998. 159: 408.
<https://www.ncbi.nlm.nih.gov/pubmed/9649250>
39. Ryu, J., *et al.* MR imaging of the male and female urethra. *Radiographics*, 2001. 21: 1169.
<https://www.ncbi.nlm.nih.gov/pubmed/11553824>
40. Stewart, S.B., *et al.* Imaging tumors of the penis and urethra. *Urol Clin North Am*, 2010. 37: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/20674692>
41. Picozzi, S., *et al.* Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. *J Urol*, 2012. 188: 2046.
<https://www.ncbi.nlm.nih.gov/pubmed/23083867>
42. Dayyani, F., *et al.* Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. *Urol Oncol*, 2013. 31: 1171.
<https://www.ncbi.nlm.nih.gov/pubmed/22534087>
43. Gakis, G., *et al.* Prognostic factors and outcomes in primary urethral cancer: results from the international collaboration on primary urethral carcinoma. *World J Urol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25981402>
44. Carroll, P.R., *et al.* Surgical anatomy of the male and female urethra. *Urol Clin North Am*, 1992. 19: 339.
<https://www.ncbi.nlm.nih.gov/pubmed/1574824>
45. Sharp, D., *et al.*, Surgery of penile and urethral carcinoma, in Campbell's Urology, D. McDougal, A. Wein, L. Kavoussi, A. Novick, A. Partin, C. Peters & P. Ramchandani, Editors. 212, Saunders Elsevier: Philadelphia, PA, USA.
46. Garden, A.S., *et al.* Primary carcinoma of the female urethra. Results of radiation therapy. *Cancer*, 1993. 71: 3102.
<https://www.ncbi.nlm.nih.gov/pubmed/8490839>
47. Champ, C.E., *et al.* Prognostic factors and outcomes after definitive treatment of female urethral cancer: a population-based analysis. *Urology*, 2012. 80: 374.
<https://www.ncbi.nlm.nih.gov/pubmed/22857759>
48. Gakis, G., *et al.* Impact of salvage surgery and radiotherapy on overall survival in patients with recurrent primary urethral cancer. *J Clin Oncol (Meeting Abstracts)*, 2015. 33: 4568.
http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/4568
49. Dalbagni, G., *et al.* Male urethral carcinoma: analysis of treatment outcome. *Urology*, 1999. 53: 1126.
<https://www.ncbi.nlm.nih.gov/pubmed/10367840>
50. Smith, Y., *et al.* Penile-preserving surgery for male distal urethral carcinoma. *BJU Int*, 2007. 100: 82.
<https://www.ncbi.nlm.nih.gov/pubmed/17488307>
51. Pedrosa, J.A., *et al.* Distal urethrectomy for localized penile squamous carcinoma *in situ* extending into the urethra: an updated series. *Int Urol Nephrol*, 2014. 46: 1551.
<https://www.ncbi.nlm.nih.gov/pubmed/24633698>

52. Kulkarni, M., *et al.* MP10-16 Substitution urethroplasty for treatment of distal urethral carcinoma and carcinoma *in situ*. J. Urol 193: e117.
<http://dx.doi.org/10.1016/j.juro.2015.02.417>
53. Dimarco, D.S., *et al.* Surgical treatment for local control of female urethral carcinoma. Urol Oncol, 2004. 22: 404.
<https://www.ncbi.nlm.nih.gov/pubmed/15464921>
54. DiMarco, D.S., *et al.* Outcome of surgical treatment for primary malignant melanoma of the female urethra. J Urol, 2004. 171: 765.
<https://www.ncbi.nlm.nih.gov/pubmed/14713806>
55. Shim, J.S., *et al.* Anterior urethrectomy for primary carcinoma of the female urethra mimicking a urethral caruncle. Int Neurourol J, 2013. 17: 197.
<https://www.ncbi.nlm.nih.gov/pubmed/24466468>
56. Milosevic, M.F., *et al.* Urethral carcinoma in women: results of treatment with primary radiotherapy. Radiother Oncol, 2000. 56: 29.
<https://www.ncbi.nlm.nih.gov/pubmed/10869752>
57. Gakis, G., *et al.* Impact of perioperative chemotherapy on survival in patients with advanced primary urethral cancer: results of the international collaboration on primary urethral carcinoma. Ann Oncol, 2015. 26: 1754.
<https://www.ncbi.nlm.nih.gov/pubmed/25969370>
58. Kent, M., *et al.* Combined chemoradiation as primary treatment for invasive male urethral cancer. J Urol, 2015. 193: 532.
<https://www.ncbi.nlm.nih.gov/pubmed/25088950>
59. Gakis, G. Editorial Comment to Docetaxel, cisplatin and 5-fluorouracil chemotherapy with concurrent radiation for unresectable advanced urethral carcinoma. Int J Urol, 2014. 21: 424.
<https://www.ncbi.nlm.nih.gov/pubmed/24251884>
60. Itoh, J., *et al.* Docetaxel, cisplatin and 5-fluorouracil chemotherapy with concurrent radiation for unresectable advanced urethral carcinoma. Int J Urol, 2014. 21: 422.
<https://www.ncbi.nlm.nih.gov/pubmed/24251859>
61. Hara, I., *et al.* Successful treatment for squamous cell carcinoma of the female urethra with combined radio- and chemotherapy. Int J Urol, 2004. 11: 678.
<https://www.ncbi.nlm.nih.gov/pubmed/15285764>
62. Cohen, M.S., *et al.* Coordinated chemoradiation therapy with genital preservation for the treatment of primary invasive carcinoma of the male urethra. J Urol, 2008. 179: 536.
<https://www.ncbi.nlm.nih.gov/pubmed/18076921>
63. Palou Redorta, J., *et al.* Intravesical instillations with bacillus calmette-guerin for the treatment of carcinoma *in situ* involving prostatic ducts. Eur Urol, 2006. 49: 834.
<https://www.ncbi.nlm.nih.gov/pubmed/16426729>
64. Taylor, J.H., *et al.* Long-term follow-up of intravesical bacillus Calmette-Guerin treatment for superficial transitional-cell carcinoma of the bladder involving the prostatic urethra. Clin Genitourin Cancer, 2007. 5: 386.
<https://www.ncbi.nlm.nih.gov/pubmed/17956711>
65. Gofrit, O.N., *et al.* Prostatic urothelial carcinoma: is transurethral prostatectomy necessary before bacillus Calmette-Guerin immunotherapy? BJU Int, 2009. 103: 905.
<https://www.ncbi.nlm.nih.gov/pubmed/19021623>
66. Njinou Ngninkeu, B., *et al.* Transitional cell carcinoma involving the prostate: a clinicopathological retrospective study of 76 cases. J Urol, 2003. 169: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/12478124>
67. Palou, J., *et al.* Urothelial carcinoma of the prostate. Urology, 2007. 69: 50.
<https://www.ncbi.nlm.nih.gov/pubmed/17280908>
68. Hillyard, R.W., Jr., *et al.* Superficial transitional cell carcinoma of the bladder associated with mucosal involvement of the prostatic urethra: results of treatment with intravesical bacillus Calmette-Guerin. J Urol, 1988. 139: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/3339727>
69. Solsona, E., *et al.* The prostate involvement as prognostic factor in patients with superficial bladder tumors. J Urol, 1995. 154: 1710.
<https://www.ncbi.nlm.nih.gov/pubmed/7563328>
70. Vazina, A., *et al.* Stage specific lymph node metastasis mapping in radical cystectomy specimens. J Urol, 2004. 171: 1830.
<https://www.ncbi.nlm.nih.gov/pubmed/15076287>

10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/primary-urethral-carcinoma/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer

N. Mottet (Chair), J. Bellmunt, E. Briers (Patient Representative),
M. Bolla, L. Bourke, P. Cornford (Vice-chair), M. De Santis,
A.M. Henry, S. Joniau, T.B. Lam, M.D. Mason, H.G. van der Poel,
T.H. van der Kwast, O. Rouvière, T. Wiegel
Guidelines Associates: N. Arfi, R.C.N. van den Bergh,
T. van den Broeck, M. Cumberbatch, N. Fossati, T. Gross,
M. Lardas, M. Liew, P. Moldovan, I.G. Schoots, P.M. Willemse



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1. INTRODUCTION

1.1 Aims and scope

The Prostate Cancer (PCa) Guidelines Panel have prepared this guidelines document to assist medical professionals in the evidence-based management of PCa.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The PCa Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, radiologists, a pathologist and a patient representative.

All imaging sections in the text have been developed, jointly with the European Society of Urogenital Radiology (ESUR). Representatives of ESUR in the PCa Guidelines Panel are (in alphabetical order): Prof.Dr. O Rouvière and Dr. I.G. Schoots.

Section 6.3: Treatment - Definitive Radiotherapy, has been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO in the PCa Guidelines Panel are (in alphabetical order): Prof.Dr. M. Bolla, Prof.Dr. A.M. Henry, Prof.Dr. M.D. Mason and Prof.Dr. T. Wiegel.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/prostatecancer/?type=panel>.

1.2.1 Acknowledgement

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1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available [1, 2] as are a number of translations of all versions of the PCa Guidelines. All documents can be accessed on the EAU website: <http://uroweb.org/guideline/prostate-cancer/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU PCa Guidelines were first published in 2001. This 2017 document presents a full update of the 2016 full text document.

1.4.2 Summary of changes

New and relevant evidence has been identified, collated and appraised through a structured assessment of the literature and incorporated in all chapters of the 2017 EAU PCa Guidelines.

Key changes for the 2017 print:

- Chapter 3 - Epidemiology and aetiology. This section has been completely renewed.
- Chapter 4 - Classification and staging systems. This chapter has been expanded with a new section (4.3 Prognostic relevance of stratification). Additional information on the International Society of Urological Pathology Gleason grading has been included in Table 4.2.2 (EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer).
- Section 6.6.8 - Imaging as marker of response in metastatic prostate cancer. This is a new section.
- Chapter 6.7 - Management of PCa in older men. Two new figures have been included.
- Chapter 8 - Quality of life outcomes in prostate cancer. This chapter is partly based on the findings of a new systematic review (SR) (see below). A second review is ongoing, the findings of which will be incorporated in the 2018 print of these Guidelines.

Changes in the summaries of evidence and recommendations can be found in sections:

3.2.3 Summary of evidence and guidelines for epidemiology and aetiology

Summary of evidence
Prostate cancer is a major health issue in men, the incidence mainly dependent on age.
Genetic factors are associated with risk of (aggressive) PCa but ongoing trials will need to define the clinical applicability of screening for genetic susceptibility of PCa.
A variety of exogenous/environmental factors may have an impact on the risk of progression.
5-ARIs are not EMA-approved for PCa prevention.
Selenium or vitamin-E supplements have no beneficial effect in preventing PCa.
In hypogonadal men, testosterone supplementation does not increase the risk of PCa.

Recommendation
No definitive recommendation can be provided for specific preventive or dietary measures to reduce the risk of developing prostate cancer.

Table 4.2.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	Intermediate-risk	High-risk	
PSA < 10 ng/mL and GS < 7 (ISUP Grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP Grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP Grade 4/5) or cT2c	any PSA any GS cT3-4 or cN+ Any ISUP Grade
Localised			Locally advanced

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

6.1.5 Guidelines for active surveillance and watchful waiting

Recommendations - active surveillance	LE	GR
Perform multiparametric magnetic resonance imaging before a confirmatory biopsy.	2b	B
During confirmatory biopsy include systematic and targeted biopsies.	2a	B

6.2.7.5 Guidelines for eLND in prostate cancer and pN+ patients

Recommendation	LE	GR
Do not perform a frozen section of nodes during radical prostatectomy to decide whether to proceed with, or abandon, the procedure.	2a	A

6.2.10 Guidelines for radical prostatectomy

Recommendations	LE	GR
Offer both radical prostatectomy and radiotherapy in patients with low- and intermediate-risk disease and a life expectancy > 10 years.	1b	A
Offer active surveillance as an alternative to surgery in patients with low-risk disease and a life expectancy of > 10 years.	1b	A

6.3.8 Summary of evidence and guidelines for definitive radiotherapy

Summary of evidence	LE
The optimum duration of androgen deprivation therapy (ADT) with external beam radiation therapy (EBRT) is well established in the literature. There is no evidence that these durations should change when using brachytherapy boost with EBRT.	1b
Limited data, from experienced centres only, are available for the use of fractionated high-dose-rate brachytherapy as monotherapy in patients with low and intermediate-risk PCa.	2a

Recommendations	LE	GR
Moderate hypofractionation (HFX) with IMRT including image-guided radiation therapy (IGRT) to the prostate only can be offered to carefully selected patients with localised disease (as discussed in the text).	1a	A
Moderate HFX should adhere to radiotherapy-protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.	1a	A

6.9.4.6 Guidelines for imaging in patients with biochemical recurrence

Prostate-specific antigen (PSA) recurrence after radical prostatectomy	LE	GR
PSA \geq 1 ng/mL: positron emission tomography (PET)/computed tomography (CT) imaging is recommended using choline or prostate-specific membrane antigen (PMSA).	2b	A

8.3.1.1 Guidelines for long term quality of life in men with localised disease

Recommendations	LE	GR
Advise eligible patients for active surveillance, that global quality of life is equivalent for up to five years compared to radical prostatectomy or radiotherapy.	1b	A
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of radiotherapy on bowel function with patients.	1b	A
Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after five years.	1b	C

8.3.2.1 Guidelines on improving quality of life in men who have been diagnosed with prostate cancer

Recommendations	LE	GR
Offer men on androgen deprivation therapy, twelve weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	1a	A
Offer men with T1-T3 disease specialist nurse led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	1b	A

2. METHODS

2.1 Data identification

For the 2017 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive literature search, covering all sections of the PCa Guidelines was performed. The search was limited to studies representing only high levels of evidence (i.e. SRs with meta-analysis, randomised controlled trials (RCTs), and prospective comparative studies) published in the English language. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time

frame between June 1st 2015 to June 23rd, 2016. A total of 1,914 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <http://uroweb.org/guideline/prostatecancer/?type=appendices-publications>.

Specific sections of the text have been updated based on a SR questions prioritised by the Guidelines Panel. These reviews were performed using standard Cochrane systematic review methodology; <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>:

- What is the negative predictive value of multiparametric MRI in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the EAU Prostate Cancer Guidelines Panel [prior to print] [3].
- The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A systematic review [4].
- Systematic review of quality of life outcomes as assessed by PROMS following primary treatment of clinically localised prostate cancer.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address. In addition, the International Society of Geriatric Oncology (SIOG), the European Society for Radiotherapy & Oncology (ESTRO) and the European Society for Urogenital Radiology (ESUR) have endorsed the PCa Guidelines.

2.2 Review

Publications ensuing from the systematic reviews have all been peer-reviewed. The following sections were subjected to peer review prior to publication:

All Imaging sections:

- Section 5.2.3 - The role of imaging in PCa diagnosis;
- Section 5.3 - The role of imaging in clinical staging;
- Section 6.1.2.1 - The role of multiparametric magnetic resonance imaging in active surveillance
- Section 6.6.8 (new section) - Imaging as a marker of response in metastatic PCa,
- Sections 6.10.4 and 6.10.5 - The role of imaging in PSA-only recurrence after treatment with curative intent.
- Section 6.10 – Treatment - Management of PSA-only recurrence after treatment with curative intent.
- Section 6.10 – Treatment – Castration-resistant PCa

2.3 Future goals

The results of ongoing and new SRs will be included in the 2017 update of the PCa Guidelines.

Ongoing SRs:

- How does biochemical recurrence following curative treatment for prostate cancer impact on overall survival, cancer-specific survival and development of metastatic disease? [6].
- What evidence based supportive interventions improve disease-specific quality of life in men with prostate cancer?

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Prostate cancer remains the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed [7]. The frequency of autopsy-detected PCa is roughly the same worldwide [8]. A SR of autopsy studies showed a prevalence of PCa at age < 30 years of 5% (95% CI: 3-8%), increasing by an odds ratio of 1.7 (1.6-1.8) per decade, to a prevalence of 59% (48-71%) by age > 79 years [9].

The incidence of PCa diagnosis, however, varies widely between different geographical areas, being highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] of 111.6 and 97.2 per 100,000, respectively), and in Western and Northern Europe (ASR 94.9 and 85), largely due to the use of prostate specific antigen (PSA) testing and the aging population. The incidence is low in Eastern and South-

Central Asia (ASR 10.5 and 4.5), whilst rates in Eastern and Southern Europe, which were low, have showed a steady increase [7, 8].

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (Caribbean, 29 per 100,000 and Sub-Saharan Africa, ASRs 19-24 per 100,000), intermediate in the USA and very low in Asia (2.9 per 100,000 in South-Central Asia) [7].

3.2 Aetiology

3.2.1 Family history/genetics

Family history and racial/ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [10, 11]. However, only a small subpopulation of men with PCa (~9%) have true hereditary disease. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset PCa (< 55 years) [11]. Patients with hereditary PCa usually have a disease onset six-seven years earlier than average, but their clinical course does not seem to differ in other ways, e.g. for disease aggressiveness [11, 12]. Men with African ethnicity origin show a higher incidence of PCa and generally have a more lethal course of disease [13].

Of the underlying determinants of genomic diversity and mechanisms between genetic and environmental factors, much remains unknown. Genome-wide association studies have identified 100 common susceptibility loci contributing to the risk for PCa, explaining ~38.9% of the familial risk for this disease [14, 15]. Furthermore, an incidence was found of 11.8% of germline mutations in genes mediating DNA-repair processes among men with metastatic PCa [16]. Germline mutations in genes such as HOXB13 and BRCA1/2 have been associated with an increased risk of PCa, targeted genomic analysis of these genes could offer options to identify families at high risk [17, 18]. Trials of screening for PCa-targeting BRCA mutation carriers are ongoing [19].

3.2.2 Risk factors

As Japanese men move from Japan to California, their risk of PCa increases, approaching that of American men [20]. A wide variety of exogenous/environmental factors have been discussed as being aetiologically important for the risk of progression from latent to clinical PCa [21]. However, currently there are no effective preventative dietary or pharmacological interventions.

3.2.2.1 Metabolic syndrome (MetS)

The single components hypertension ($p = 0.035$) and waist circumference > 102 cm ($p = 0.007$) of MetS have been associated with a significantly greater risk of PCa, but conversely, having ≥ 3 components of MetS is associated with a reduced risk (odds ratio [OR]: 0.70 95%; CI: 0.60-0.82) [22, 23].

3.2.2.1.1 Diabetes/metformin

On a population level, metformin users (but not other oral hypoglycaemics) were found to be at a decreased risk of PCa diagnosis, compared with never-users (adjusted OR: 0.84; 95% CI: 0.74-0.96) [24]. In 540 diabetic participants of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, metformin use was not significantly associated with PCa (OR: 1.19; $p = 0.50$) [25].

3.2.2.1.2 Cholesterol/statins

A meta-analysis of fourteen large prospective studies did not show an association between blood total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) levels and the risk of either overall PCa or high-grade PCa [26]. Results of the REDUCE study also did not show a preventive effect of statins on PCa risk [25].

3.2.2.1.3 Obesity

Within the REDUCE study, obesity was associated with lower risk of low-grade PCa in multivariable analyses (OR: 0.79; $p = 0.01$), but increased risk of high-grade PCa (OR, 1.28; $p = 0.042$) [27]. This effect seems mainly explained by environmental determinants of height/BMI rather than genetically elevated height or BMI [28].

3.2.2.2 Dietary factors

The association between a wide variety of dietary factors and PCa have been studied (Table 3.1).

Table 3.1: Dietary factors that have been associated with prostate cancer

Alcohol	High alcohol intake, but also total abstinence from alcohol have been associated with a higher risk of PCa and PCa-specific mortality [29].
Dairy	A weak correlation between insulin-like growth factor-I (IGF-1) levels and high intake of protein from dairy products and the risk of PCa was found [30].
Fat	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [31]. A relation between intake of fried foods and risk of PCa may exist [32].
Lycopene (carotenes)	A trend towards a favourable effect of lycopene on PCa incidence has been identified in meta-analyses [33], RCTs comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [34].
Meat	A meta-analysis did not show an association between red meat or processed meat consumption and PCa [35].
Vitamin D (25(OH)D)	An U-shaped association has been observed, with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease [36, 37].
Selenium/Vitamin E	Selenium and Vitamin E were found not to affect PCa incidence [38].

3.2.2.3 *Hormonally active medication*

3.2.2.3.1 5-alpha-reductase inhibitors (5-ARIs)

Although it seems that 5-ARIs have the potential of preventing or delaying the development of PCa (~25%, for Gleason 6 cancer only), this must be weighed against treatment-related side effects as well as the potential small increased risk of high-grade PCa [39-41]. None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for this indication.

3.2.2.3.2 Testosterone

Hypogonadal men receiving testosterone supplementation did not have an increased risk of PCa [42].

3.2.2.4 *Other risk factors*

Balding was associated with a higher risk of PCa death [43]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR:1.31; 95% CI: 1.14-1.52) [44]. Occupational exposure may also play a role, based on a meta-analysis, night-shift work is associated with an increased risk (2.8%; $p = 0.030$) of PCa [45]. Pilots also have been found to have an increased risk of PCa diagnosis (RR 2.0) [46]. Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24; 95% CI: 1.18-1.31) [47].

In contradiction, vasectomy was not associated with an increased risk of PCa [48]. No association between self-reported acne and risk of (aggressive) PCa was found [49]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa [50, 51].

Ultraviolet radiation exposure decreased the risk of PCa (hazard ratio [HR]: 0.91; 95% CI: 0.88-0.95) [52]. A protective effect for PCa of circumcision was found [53]. Higher ejaculation frequency (≥ 21 times a month versus 4-7 times) has been associated with a 20% lower risk of PCa [54].

3.2.3 **Summary of evidence and guidelines for epidemiology and aetiology**

Summary of evidence
Prostate cancer is a major health issue in men, the incidence mainly dependent on age.
Genetic factors are associated with risk of (aggressive) PCa but ongoing trials will need to define the clinical applicability of screening for genetic susceptibility of PCa.
A variety of exogenous/environmental factors may have an impact on the risk of progression.
5-ARIs are not EMA-approved for PCa prevention.
Selenium or vitamin-E supplements have no beneficial effect in preventing PCa.
In hypogonadal men, testosterone supplementation does not increase the risk of PCa.

Recommendation
No definitive recommendation can be provided for specific preventive or dietary measures to reduce the risk of developing prostate cancer.

4. CLASSIFICATION AND STAGING SYSTEMS

4.1 Classification

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for the design of clinical trials on relatively homogeneous patient populations, the comparison of clinical and pathological data obtained from different hospitals across the world, and the formulation of recommendations for the treatment of these patient populations. Throughout these Guidelines the 2017 Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1.1) [55] and the EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, are used (Table 4.2.2) [56]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after surgery or external beam radiotherapy (EBRT).

Table 4.1.1: Tumour Node Metastasis (TNM) classification of PCa [55]

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is not palpable
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)
T2	Tumour that is palpable and confined within the prostate
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule ¹
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional Lymph Nodes²	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant Metastasis³	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

¹Invasion into the prostate apex or into (but not beyond) the prostate capsule is not classified as T3, but as T2.

²Metastasis no larger than 0.2 cm can be designated pNmi.

²T2a to c only exist for clinical T2 (cT2). For pathological T2 they are no longer present in the 2017 TNM. Only pT2 exists.

³When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

4.2 Gleason score and International Society of Urological Pathology 2014 grade groups

The 2005 International Society of Urological Pathology (ISUP) modified Gleason score of biopsy-detected PCa comprises the Gleason grade or the most extensive (primary pattern) pattern, plus the second most common pattern (secondary pattern), if two are present. If one pattern is present, it needs to be doubled to yield the Gleason score. For three grades, the Gleason score comprises the most common grade plus the highest grade, irrespective of its extent. When a carcinoma is largely grade 4/5, identification of < 5% of Gleason grade 2 or 3 glands should not be incorporated in the Gleason score. A Gleason score ≤ 4 should not be given based on prostate biopsies [57]. In addition to reporting of the carcinoma features for each biopsy, an overall (or global) Gleason score based on the carcinoma-positive biopsies can be provided. The 2014 ISUP Gleason grading conference of prostatic carcinoma [58, 59] limits the number of PCa grades, ranging them from 1 to 5 (see table 4.2.1), in order to:

1. align the PCa grading with the grading of other carcinomas;

2. eliminate the anomaly that the most highly differentiated PCas have a Gleason score 6;
3. to further define the clinically highly significant distinction between Gleason score 7 (3 + 4) and 7 (4 + 3) PCa.

The ISUP 2014 Gleason grading represents a compression of Gleason scores ≤ 6 to ISUP grade 1, and Gleason scores 9-10 to ISUP grade 5, whereas Gleason score 7 is expanded to ISUP grade 2, i.e. 7 (3 + 4) and ISUP grade 3, i.e. 7 (4 + 3).

Table 4.2.1: International Society of Urological Pathology 2014 grades

Gleason score	ISUP grade
2-6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4 or 3 + 5 or 5 + 3)	4
9-10	5

Table 4.2.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	Intermediate-risk	High-risk	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS cT3-4 or cN+ Any ISUP grade
Localised			Locally advanced

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

4.3 Prognostic relevance of stratification

A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management. The adoption of the current ISUP grading system, defining the split-up of Gleason score 7 cancers into ISUP grade 2 (primary Gleason grade 3) and ISUP 3 (primary Gleason grade 4) because of their distinct prognostic impact [59] strengthens such a separation of the intermediate-risk group into a low-intermediate (ISUP grade 2) and high intermediate-risk (ISUP grade 3) group. Emerging clinical data support this distinction between favourable- and unfavourable-risk patient categories within the intermediate-risk group [60].

5. DIAGNOSTIC EVALUATION

5.1 Screening and early detection

Population or mass screening is defined as the 'systematic examination of asymptomatic men (at risk)' and is usually initiated by health authorities. In contrast, early detection or opportunistic (*ad-hoc*) testing consists of individual case findings, which are initiated by the man being tested (patient) and/or his physician. The co-primary objectives of both strategies are:

- reduction in mortality due to PCa;
- at least, a maintained quality of life (QoL) as expressed by QoL-adjusted gain in life years (QUALYs).

Prostate cancer mortality trends range widely from country to country in the industrialised world [61]. Mortality due to PCa has decreased in most Western countries but the magnitude of the reduction varies between countries. The reduced mortality rate seen recently in the USA is considered to be partly due to a widely adopted aggressive PCa screening policy [62]. However, there is still no level 1 evidence that PSA mass screening is cost-effective in reducing PCa mortality [63].

Currently, screening for PCa is one of the most controversial topics in the urological literature [64]. Three large

prospective RCTs published data on screening in 2009 [65-67]. Heated discussions and debates resulted in many conflicting positions and policy papers. Some authors argue that following the current American Urological Association (AUA) guidelines [68] or the US Preventive Services Task Force recommendations for screening [69] may lead to a substantial number of men with aggressive disease being missed [70, 71]. A comparison of systematic and opportunistic screening suggested over-diagnosis and mortality reduction in the systematic screening group compared to a higher over-diagnosis with a marginal survival benefit, at best, in the opportunistic screening regimen [72]. The potential impact of this topic would necessitate the highest level of evidence produced through a systematic literature search of all published trials or cohorts summarised in a meta-analysis. Subgroup analyses of cohorts that are part of large trials, or mathematical projections alone, cannot provide the quality of evidence needed to appropriately address this clinical question.

A Cochrane review published in 2013 [63], which has been updated since [73] presents the main overview of the date. The findings of the updated publication (based on a literature search until April 3, 2013) are almost identical to the 2013 review:

- Screening is associated with an increased diagnosis of PCa (RR: 1.3; 95% CI: 1.02-1.65).
- Screening is associated with detection of more localised disease (RR: 1.79; 95% CI: 1.19-2.70) and less advanced PCa (T3-4, N1, M1) (RR: 0.80; 95% CI: 0.73-0.87).
- From the results of five RCTs, randomising more than 341,000 men, no PCa-specific survival benefit was observed (RR: 1.00; 95% CI: 0.86-1.17). This was the main endpoint in all trials.
- From the results of four available RCTs, no overall survival (OS) benefit was observed (RR: 1.00; 95% CI: 0.96-1.03).

Moreover, screening was associated with minor and major harms such as over-diagnosis and over-treatment. Surprisingly, the diagnostic tool (i.e. biopsy) was not associated with any mortality in the selected papers, which is in contrast with other known data [40, 41].

The impact on the patient's overall QoL is still unclear [74-76], but screening has never been shown to be detrimental at population level. All these findings have led to strong advice against systematic population-based screening in all countries, including Europe.

Since 2013, the European Randomized Study of Screening for Prostate Cancer (ERSPC) data have been updated with 13 years of follow up (see Table 5.1.1) [77]. The key message is that with extended follow up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However the number needed to screen and to treat is decreasing, and is now below the number needed to screen observed in breast cancer trials [78].

Table 5.1.1: Follow-up data from the ERSPC study [77]

Years of follow-up	Number needed to screen	Number needed to treat
9	1,410	48
11	979	35
13	781	27

An individualised risk-adapted strategy for early detection might be offered to a well-informed man with at least ten-fifteen years of life expectancy. However, this approach may still be associated with a substantial risk of over-diagnosis. It is therefore important to carefully identify the patient cohorts likely to benefit most from individual early diagnosis, taking into account the potential balances and harms involved.

Men at elevated risk of having PCa are those > 50 years, or at age > 45 years with a family history of PCa (both paternal or maternal [79]), or African-Americans [80]. In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [81, 82] are also at increased risk of PCa metastasis or death from PCa several decades later. The long-term survival and QoL benefits of such an approach remains to be proven at a population level. In 2014, as for breast cancer, a genetic abnormality associated with an increased risk has been shown prospectively i.e. BRCA2 [19, 83]. Several new biological markers such as TMPRSS2-Erg fusion, PCA3 [84, 85] or kallikreins as incorporated in the Phi or 4Kscore tests [86, 87] have been shown to add sensitivity and specificity on top of PSA, potentially avoiding unnecessary biopsies and lowering over-diagnosis. At this time there is too limited data to base a recommendation on.

Risk calculators may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. Several tools developed from cohort studies are available:

- from the PCPT cohort: PCPTRC 2.0 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>;
 - from the ERSPC cohort: <http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-riskcalculators>;
 - from a local Canadian cohort: <http://sunnybrook.ca/content/?page=occ-prostatecalc> (among others).
- Since none has clearly shown superiority it remains a personal decision which one to use [88].

Informed men requesting an early diagnosis should be given a PSA test and undergo a digital rectal examination (DRE) [89]. The optimal intervals for PSA testing and DRE follow-up are unknown, as they varied between several prospective trials. A risk-adapted strategy might be considered based on the initial PSA level. This could be every two years for those initially at risk, or postponed up to eight to ten years in those not at risk [90].

The age at which early diagnosis should be stopped remains controversial, but an individual's life expectancy must definitely be taken into account. Men who have less than a fifteen-year life expectancy are unlikely to benefit based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the ERSPC trials. Furthermore, although there is no simple tool to evaluate individual life expectancy, co-morbidity is at least as important as age. A detailed review can be found in Section 6.7 on senior adults and in the recently updated SIOG Guidelines [91].

Based on the tools currently available, an individualised strategy will diagnose many insignificant lesions (over 50% in some trials), most of which will not require any form of active treatment (see Section 6.1 - Deferred treatment). It is important to realise that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.

5.1.1 **Guidelines for screening and early detection**

Recommendations	LE	GR
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	3	B
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life-expectancy of at least ten to fifteen years.	3	B
Offer early PSA testing in well-informed men at elevated risk of having PCa: <ul style="list-style-type: none"> • men > 50 years of age; • men > 45 years of age and a family history of PCa; • African-Americans > 45 years of age; • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age. 	2b	A
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk: <ul style="list-style-type: none"> • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to eight years in those not at risk.	3	C
Decide on the age at which early diagnosis of PCa should be stopped based on life expectancy and performance status; men who have a life-expectancy of < 15-years are unlikely to benefit.	3	A

5.2 **Clinical diagnosis**

Prostate cancer is usually suspected on the basis of DRE and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from transurethral resection of the prostate (TURP) or prostatectomy for benign prostatic enlargement (BPE).

5.2.1 **Digital rectal examination**

Most PCas are located in the peripheral zone and may be detected by DRE when the volume is ≥ 0.2 mL. In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [92]. Suspect DRE in patients with PSA level ≤ 2 ng/mL has a positive predictive value of 5-30% [93]. Abnormal DRE is associated with an increased risk of higher Gleason score and is an indication for biopsy [94, 95].

5.2.2 **Prostate-specific antigen**

The use of PSA as a serum marker has revolutionised PCa diagnosis [96]. Prostate-specific antigen is organ- but not cancer-specific, therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and

other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS) [97].

There are no agreed standards defined for measuring PSA [98]. PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [99]. Table 5.2.1 demonstrates the occurrence of Gleason ≥ 7 (or ISUP grade 2) PCa at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but clinically significant PCa. The use of nomograms may help in predicting indolent PCa [100].

Table 5.2.1: Risk of PCa in relation to low PSA values

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason ≥ 7 PCa (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

5.2.2.1 PSA density

Prostate specific antigen density is the level of serum PSA divided by the TRUS-determined prostate volume. The higher the PSA density, the more likely it is that the PCa is clinically significant (see Section 6.1.3).

5.2.2.2 PSA velocity and doubling time

There are two methods of measuring PSA kinetics:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [101];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [102].

Prostate specific antigen velocity and PSA-DT may have a prognostic role in treating PCa [103], but limited diagnostic use because of background noise (total prostate volume, and BPH), different intervals between PSA determinations, and acceleration/deceleration of PSAV and PSA-DT over time. These measurements do not provide additional information compared with PSA alone [104-107].

5.2.2.3 Free/total PSA ratio

Free/total (f/t) PSA ratio can be used to differentiate BPH from PCa. It stratifies the risk of PCa in men with 4-10 ng/mL total PSA and negative DRE. Prostate cancer was detected by biopsy in 56% of men with f/t PSA < 0.10 , but in only 8% with f/t PSA > 0.25 ng/mL [108]. Free/total PSA is of no clinical use if total serum PSA is > 10 ng/mL or during follow up of known PCa.

Free/total PSA must be used cautiously because it may be adversely affected by several pre-analytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates) [109].

5.2.2.4 Additional serum testing

A few assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the FDA-approved Prostate Health Index (PHI) test, combining free and total PSA and the (-2)pro-PSA isoform (p2PSA), and the four kallikrein (4K) score test (measuring free, intact and total PSA and kallikrein-like peptidase 2 [hK2]). Both tests are intended to reduce the number of unnecessary prostate biopsies in PSA-tested men. A few prospective multicentre studies demonstrated that both the PHI and 4K test out-performed f/t PSA PCa detection, with an improved prediction of clinically significant PCa in men with a PSA between 2-10 ng/mL [87, 110] [111]. In a head to head comparison both tests performed equally [112].

5.2.2.5 PCA3 marker

Prostate cancer gene 3 (PCA3) is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The commercially available ProgenSA urine test for PCA3 is superior to total and percent-free PSA for detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve for positive biopsies [113-116].

PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts Gleason score, and its use for monitoring in active surveillance (AS) is, as yet, not confirmed [117]. Currently, the main indication for the ProgenSA test is to determine whether repeat biopsy is needed after an initially negative biopsy, but its clinical effectiveness for this purpose is uncertain [118].

5.2.2.6 Guidelines for risk-assessment of asymptomatic men

Recommendations	LE	GR
In order to avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a prostate specific antigen level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: <ul style="list-style-type: none"> risk-calculator; an additional serum or urine-based test (e.g. Prostate Health Index test [PHI], four kallikrein [4K]score or Prostate cancer gene 3 [PCA3]) or imaging. 	3	C

5.2.3 Prostate biopsy

5.2.3.1 Baseline biopsy

The need for prostate biopsy is based on PSA level and/or suspicious DRE. Age, potential comorbidity, and therapeutic consequences should also be considered and discussed beforehand [119]. Risk stratification is a potential tool for reducing unnecessary biopsies [119].

Limited PSA elevation alone should not prompt immediate biopsy. Prostate specific antigen level should be verified after a few weeks using the same assay under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections [UTIs]) in the same laboratory [120, 121]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [122].

Ultrasound (US)-guided biopsy is now the standard of care. A transrectal approach is used for most prostate biopsies, although some urologists prefer a perineal approach. Cancer detection rates are comparable with both approaches [123, 124].

5.2.3.2 Repeat biopsy after previously negative biopsy

The indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.2.1 for risk estimates);
- suspicious DRE, 5-30% cancer risk [92, 93];
- atypical small acinar proliferation (i.e., atypical glands suspicious for cancer), 40% risk [125];
- extensive (multiple biopsy sites, i.e., ≥ 3) high-grade prostatic intraepithelial neoplasia (HGPIN), ~30% risk [125, 126];
- a few atypical glands immediately adjacent to high-grade prostatic intraepithelial neoplasia (i.e., PINATYP), ~50% risk [127];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade prostate carcinoma [128];
- positive multiparametric magnetic resonance imaging (mpMRI) findings (see Section 5.2.4).

Additional information may be gained by the ProgenSA DRE urine test for PCA3, the serum 4Kscore and PHI tests or a tissue-based epigenetic test (ConfirmMDx). The role of PHI and ProgenSA PCA3 in deciding whether to take a repeat biopsy in men who had a previous negative biopsy is uncertain and probably not cost-effective [118]. The ConfirmMDx test is based on the concept that benign prostatic tissue in the vicinity of a PCa focus shows distinct epigenetic alterations. If, due to sampling bias, the PCa is missed at biopsy, demonstration of epigenetic changes in the adjacent benign tissue would indicate the presence of carcinoma. The ConfirmMDX test quantifies the methylation level of promoter regions of three genes (RASSF1, GSTP1 and APC) in benign prostatic tissue. A multicentre study found a negative predictive value of 88% when methylation was absent in all three markers, implying that a repeat biopsy could be avoided in these men [129]. Given the limited available data, no recommendation can be made regarding its routine application.

Table 5.2.2: Description of additional investigational tests after a negative prostate biopsy*

Name of test	Test substrate	Molecular	FDA approved
ProgenSA	DRE urine	lncRNA PCA3	yes
PHI	Serum	Total, free and p2PSA	yes
4Kscore Test	Serum/plasma	Total, free, intact PSA, hK2	no
ConfirmMDX	Benign prostate biopsy	Methylated APC, RASSF1 and GSTP1	no

*Isolated high-grade PIN in one or two biopsy sites is no longer an indication for repeat biopsy [130].

5.2.3.3 Saturation biopsy

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30-43% and depends on the number of cores sampled during earlier biopsies [131]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The high rate of urinary retention (10%) is a drawback [132].

5.2.3.4 Sampling sites and number of cores

On baseline biopsies, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland. Additional cores should be obtained from suspect areas by DRE/TRUS. Sextant biopsy is no longer considered adequate. For a prostate volume of 30-40 mL, ≥ 8 cores should be sampled. Ten to twelve core biopsies are recommended [133], with > 12 cores not being significantly more conclusive [134, 135].

5.2.3.5 Diagnostic transurethral resection of the prostate

Transurethral resection of the prostate should not be used as a tool for cancer detection [136].

5.2.3.6 Seminal vesicle biopsy

Indications for seminal vesicle (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20-25% [137]. A seminal vesicle staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent radiotherapy. Its added value compared with mpMRI is questionable.

5.2.3.7 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to repeat biopsies [138].

5.2.3.8 Antibiotics prior to biopsy

Oral or intravenous antibiotics are recommended. Quinolones are the drugs of choice, with ciprofloxacin being superior to ofloxacin [139]. Increased quinolone resistance [140] is associated with a rise in severe post-biopsy infection [141].

5.2.3.9 Local anaesthesia prior to biopsy

Ultrasound-guided periprostatic block is recommended [142]. It is not important whether the depot is apical or basal. Intrarectal instillation of local anaesthesia is inferior to periprostatic infiltration [143].

5.2.3.10 Fine-needle aspiration biopsy

Fine-needle aspiration biopsy is no longer recommended.

5.2.3.11 Complications

Biopsy complications are listed in Table 5.2.3 [144]. Severe post-procedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [145]. Low-dose aspirin is no longer an absolute contraindication [146]. A SR found favourable infections rates for transperineal compared to transrectal biopsies with similar rates of haematuria, haematospermia and urinary retention [147].

Table 5.2.3: Percentage of complications per biopsy session, irrespective of the number of cores

Complications	Percentage of patients affected
Haematospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C	0.8
Epididymitis	0.7
Rectal bleeding > 2 days +/- surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

5.2.4 The role of imaging

5.2.4.1 Transrectal ultrasound (TRUS) and ultrasound-based techniques

Grey-scale TRUS is not reliable at detecting PCa [148]. Thus, there is no evidence that US-targeted biopsies can replace systematic biopsies. New sonographic modalities such as sonoelastography and contrast-enhanced US are still under investigation. Currently there is not enough evidence for their routine use.

5.2.4.2 Multiparametric magnetic resonance imaging

Correlation with radical prostatectomy (RP) shows that mpMRI, associating T2-weighted imaging with diffusion-weighted imaging, dynamic contrast-enhanced imaging, and/or H1-spectroscopy, has good sensitivity for the detection and localisation of Gleason score ≥ 7 cancers (see Table 5.2.4) [149-152].

Table 5.2.4: PCa detection rates (%) by mpMRI for tumour volume and Gleason score in radical prostatectomy specimen [151]

Gleason score	Tumour volume (mL)		
	< 0.5	0.5-2	> 2
GS6	21-29%	43-54%	67-75%
GS7	63%	82-88%	97%
GS >7	80%	93%	100%

Multiparametric magnetic resonance imaging can reliably detect aggressive tumours in candidates for prostate biopsy with a negative (NPV) and positive predictive value (PPV) ranging from 63 to 98% and from 34 to 68%, respectively [153]. As a result, mpMRI is increasingly performed before prostate biopsy.

Theoretically, pre-biopsy mpMRI could be used in two different ways. The first strategy uses mpMRI to improve the detection of clinically significant prostate cancer (csPCa). In this diagnostic pathway, MRI-targeted biopsy (TBx) would be added to systematic biopsies in case of positive mpMRI, and systematic biopsies would be performed in all patients with negative mpMRI. The second strategy uses mpMRI as a triage test before biopsy. In this diagnostic pathway, only MRI-TBx would be performed in case of a positive mpMRI. Patients with negative mpMRI results would not undergo a prostate biopsy at all.

A large body of evidence suggests that MRI-TBx has a higher detection rate of detecting csPCa as compared to systematic biopsy [154-158]. However, sub-groups analysis showed that the impact of mpMRI was most marked in the repeat-biopsy setting, but not in biopsy-naïve men [154, 155]. Single centre RCTs performed in biopsy-naïve men provided contradictory findings as to whether or not the combination of systematic biopsies and MRI-TBx had a higher detection rate for PCa and csPCa than systematic biopsies alone [159-161]. Two large multicentre studies (MRI-FIRST and PRECISION) are currently ongoing to define the added value of pre-biopsy MRI in biopsy-naïve patients. It is therefore too early to make recommendations on the routine use of pre-biopsy mpMRI in biopsy-naïve patients.

Magnetic resonance imaging-targeted biopsies can be obtained through cognitive guidance, Ultrasound/mpMRI fusion software or direct in-bore guidance. Controlled studies and a SR did not show a clear superiority of one technique over the others [158, 162-164].

Whether systematic biopsies can be omitted in patients (or prostate lobes) with negative mpMRI depends on the NPV of mpMRI. A SR performed under the auspices of the EAU-ESTRO-ESUR-SIOG PCa Guidelines Panel showed a highly variable prevalence of overall PCa (13.0-74.7%) and csPCa (13.7-50.9%) in patients undergoing pre-biopsy mpMRI (unpublished results). Due to the fact that the NPV decreases when prevalence increases, it is necessary to risk-stratify patients before defining the patients that could safely omit biopsy in case of a negative mpMRI. Prostate-specific antigen density [165] or risk calculators [88] can be used to identify groups of patients with low risk of PCa in whom mpMRI would have a high NPV. The impact of these risk-stratification tools on the NPV of pre-biopsy mpMRI needs to be carefully evaluated, both in the biopsy-naïve and in the repeat-biopsy setting.

Despite the use of the new PIRADS v2 scoring system [166], mpMRI has a low specificity, with high rates of false positives, especially among lesions scored 3/5 and 4/5 [167]. Multiparametric magnetic resonance imaging inter-reader reproducibility is also moderate [168-171], which currently limits its broad use outside expert centres. At this moment it is too soon to define if quantitative approaches and computer-aided diagnosis systems will improve the characterisation of lesions seen at mpMRI in the future [172-174].

5.2.4.3 Guidelines for imaging

Recommendations	LE	GR
Before repeat biopsy, perform multiparametric magnetic resonance imaging (mpMRI) when clinical suspicion of PCa persists in spite of negative biopsies.	1a	A
During repeat biopsy, include systematic biopsies and targeting of any mpMRI lesions seen.	2a	B

5.2.5 Pathology of prostate needle biopsies

5.2.5.1 Processing

Prostate core biopsies from different sites are processed separately. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with the PCa detection rate [175]. To achieve optimal flattening and alignment, a maximum of three cores should be embedded per tissue cassette, and sponges or paper used to keep the cores stretched and flat [176, 177]. To optimise detection of small lesions, paraffin blocks should be cut at three levels [138] and intervening unstained sections are kept for immunohistochemistry.

5.2.5.2 Microscopy and reporting

Diagnosis of PCa is based on histology. The diagnostic criteria include features pathognomonic of cancer, major and minor features favouring cancer and features against cancer. Ancillary staining and additional (deeper) sections should be considered if a suspect lesion is identified [178-180]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [178]. Table 5.2.5 lists the recommended terminology for reporting prostate biopsies [176].

Table 5.2.5: Recommended terminology for reporting prostate biopsies [176]

Benign/negative for malignancy; if appropriate, include a description
Active inflammation
Granulomatous inflammation
High-grade prostatic intraepithelial neoplasia (PIN)
High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP)
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer
Adenocarcinoma
Intraductal carcinoma

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the ISUP 2014 Gleason grading system [181]. A global Gleason score comprising all biopsies is also reported according to the ISUP 2014 grade (see Section 4.2). Intraductal carcinoma, lymphovascular invasion (LVI) and extra-prostatic extension (EPE) must each be reported, if identified. More recently, expansile cribriform pattern of PCa as well as intraductal carcinoma in biopsies were identified as independent prognosticators of metastatic disease [182].

The proportion of carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the Gleason score, tumour volume, surgical margins and pathologic stage in RP specimens and predicts BCR, post-prostatectomy progression and RT failure. These parameters are included in nomograms created to predict pathologic stage and seminal vesicle invasion after RP and RT failure [183-185]. A pathology report should therefore provide both the proportion of carcinoma-positive cores and the extent of cancer involvement for each core. The length in mm and percentage of carcinoma in the biopsy have equal prognostic impact [186]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [187] triggering immediate treatment vs. AS in patients with Gleason score 6.

A prostate biopsy that does not contain glandular tissue should be reported as diagnostically inadequate. Mandatory elements to be reported for a carcinoma-positive prostate biopsy are:

- type of carcinoma;
- primary and secondary/worst Gleason grade (per biopsy site and global);
- percentage high-grade carcinoma (global);
- extent of carcinoma (in mm or percentage) (at least per biopsy site);
- if present: EPE, seminal vesicle invasion, LVI, intraductal carcinoma/cribriform pattern, peri-neural invasion;
- ISUP 2014 grade (global).

5.2.5.3 Tissue-based prognostic biomarker testing

The Prolaris test (Myriad Genetics) measures the expression of 31 cell-cycle associated genes in biopsy-derived PCa tissue and may be of clinical use to determine whether a patient needs curative treatment or may have his treatment deferred [188]. Similarly, Oncotype Dx is a RNA-based test based on 12 carcinoma-associated genes and 5 reference genes which can be applied to carcinoma tissue in prostate biopsies to determine the aggressiveness of the carcinoma. Both tests were shown in prospective studies to provide prognostic information in men with clinically localised PCa, additional to conventional clinico-pathological parameters, including Gleason score and PSA level. The results of prospective multicentre studies are awaited before a recommendation can be made regarding their routine application.

5.2.6 Histopathology of radical prostatectomy specimens

5.2.6.1 Processing of radical prostatectomy specimens

Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens are totally embedded, to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding may also be considered, particularly for prostates > 60 g. The most widely accepted method includes complete embedding of the posterior prostate, and a single mid-anterior left and right section. Compared with total embedding, partial embedding detected 98% of PCa with a Gleason score ≥ 7 and accurate staging in 96% of cases [189].

Ink the entire RP specimen upon receipt in the laboratory, to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before slicing. Fixation can be enhanced by injecting formalin, which provides more homogeneous fixation and sectioning after 24 hours [190]. After fixation, the apex and the base (bladder neck) are removed and cut into (para)sagittal or radial sections; the shave method is not recommended [57]. The remainder of the specimen is cut in transverse, 3-4 mm sections, perpendicular to the long axis of the urethra. The resultant tissue slices can be embedded and processed as whole-mounts or after quadrant sectioning. Whole-mounts provide better topographic visualisation, faster histopathological examination and better correlation with pre-operative imaging, although they are more time-consuming and require specialist handling. For routine sectioning, the advantages of whole mounts do not outweigh their disadvantages.

5.2.6.1.1 Guidelines for processing prostatectomy specimens

Recommendations	LE	GR
Ensure total embedding, by conventional (quadrant) or whole-mount sectioning.	3	C
Ink the entire surface before cutting, to evaluate the surgical margin.	3	A
Examine the apex and base separately, using the cone method with sagittal or radial sectioning.	3	A

5.2.6.2 Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.6). As a result of the complex information to be provided for each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.7). Synoptic reporting results in more transparent and complete pathology reporting [191].

Table 5.2.6: Mandatory elements provided by the pathology report

Histopathological type: > 95% of PCa represents conventional (acinar) adenocarcinoma.
Grading according to Gleason score (or therapy-related changes) and ISUP 2014 grade group.
Tumour (sub)staging and surgical margin status: location and extent of extraprostatic extension (EPE), presence of bladder neck invasion, laterality of EPE or seminal vesicle invasion, location and extent of positive surgical margins.
Additional information may be provided on multifocality, and diameter/volume and zonal location of the dominant tumour.

Table 5.2.7: Example checklist: reporting of prostatectomy specimens

Histopathological type
Type of carcinoma, e.g. conventional acinar, or ductal
Histological grade
Primary (predominant) Gleason grade
Secondary Gleason grade
Tertiary Gleason grade (if applicable)
Global Gleason score/ISUP 2014 grade
Approximate percentage of Gleason grade 4 or 5
Tumour quantitation (optional)
Percentage of prostate involved
Size/volume of dominant tumour nodule
Pathological staging (pTNM)
<i>If extraprostatic extension is present:</i> indicate whether it is focal or extensive; specify sites; indicate whether there is seminal vesicle invasion.
<i>If applicable, regional lymph nodes:</i> location; number of nodes retrieved; number of nodes involved.
Surgical margins
<i>If carcinoma is present at the margin:</i> specify sites.
Other
Presence of lymphovascular/angio-invasion
Location of dominant tumour
Presence of intraductal carcinoma/cribriform architecture

5.2.6.2.1 Gleason score in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2014 modified) Gleason system [181] is the strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [192].

The Gleason score is the sum of the most and second-most dominant (in terms of volume) Gleason grade. If only one grade is present, the primary grade is doubled. If a grade comprises $\leq 5\%$ of the cancer volume, it is not incorporated in the Gleason score (5% rule). The primary and secondary grades are reported in addition to the Gleason score. A global Gleason score is given for multiple tumours, but a separate tumour focus with a higher Gleason score should also be mentioned. Tertiary Gleason grade 4 or 5, particularly if $> 5\%$ of the PCa volume, is an unfavourable prognostic indicator for BCR. The tertiary grade and its approximate proportion of the cancer volume should also be reported [193] in addition to the global Gleason score as well as the ISUP 2014 grade group (see Section 4.2).

5.2.6.2.2 Definition of extraprostatic extension

Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g., neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered EPE. It is useful to report the location and extent of EPE because the latter is related to recurrence risk [194].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [195] or extension as < 1 high-power field (HPF) [196], whereas others measure the depth of extent in millimetres [197].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute EPE. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e., not as pT4, because it does not carry independent prognostic significance for PCa recurrence [198, 199] and should be recorded as EPE (pT3a). A positive margin at the bladder neck should be reported as EPE (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [200].

5.2.6.3 PCa volume

The independent prognostic value of PCa volume in RP specimens has not been established [196, 201-204]. Nevertheless, a cut-off of 0.5 mL is commonly used to distinguish insignificant from clinically relevant cancer [201]. Improvement in prostatic radio-imaging allows more accurate pre-operative measurement of cancer volume. It is recommended that at least the diameter/volume of the dominant tumour nodule should be assessed, or a rough estimate of the percentage of cancer tissue provided [205].

5.2.6.4 Surgical margin status

Surgical margin is an independent risk factor for BCR. Margin status is positive if tumour cells are in contact with the ink on the specimen surface. Margin status is negative if tumour cells are close to the inked surface [202] or at the surface of the tissue lacking ink. In tissues that have severe crush artefacts, it may not be possible to determine margin status [206].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [207]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [196]. However, some indication must be given of the multifocality extent of margin positivity, such as the linear extent in mm of involvement: focal, ≤ 1 mm vs. extensive, > 1 mm [208], or number of blocks with positive margin involvement.

5.2.7 Guidelines for the clinical diagnosis of prostate cancer

Recommendations	LE	GR
Do not use transurethral resection of the prostate as a tool for cancer detection.	2a	A
Use the International Society of Urological Pathology (ISUP) 2014 Gleason grading system for grading of PCa.	2a	A
In symptomatic men, base the initial decision to perform a biopsy on prostate-specific antigen (PSA) testing and digital rectal examination (DRE).	2b	A
Use the additional diagnostic options in asymptomatic men with a normal DRE and a PSA between 2.0 and 10 ng/mL (risk calculator, or an additional serum or urine-based test [e.g. Prostate Health Index, 4Kscore or prostate cancer gene 3] or imaging).	3	C
Do not initially offer transition zone biopsies due to low detection rates.	2b	B
For initial diagnosis, perform a core biopsy of ten to twelve systematic transrectal or transperineal peripheral zone biopsies under ultrasound guidance.	2a	B
Perform transrectal prostate needle biopsies under antibiotic protection.	1b	A
Use a local anaesthetic by periprostatic infiltration for transrectal prostate needle biopsies.	1a	A
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	3	A
Adhere to the 2010 ISUP consensus meeting Guidelines for processing and reporting of prostatectomy specimens.	3	A
Perform one set of repeat biopsies for persistent indications for PCa (abnormal DRE, elevated PSA or histopathological findings suggestive of malignancy at initial biopsy).	2a	B

5.3 Diagnosis: Clinical staging

The extent of PCa is evaluated by DRE and PSA, and may be supplemented with bone scanning and computed tomography (CT) or mpMRI.

5.3.1 T-staging

5.3.1.1 Definitions

Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that extends beyond the prostate gland (e.g., neurovascular bundle, anterior prostate, or bladder neck) and corresponds to stage T3a. It is to be distinguished from seminal vesicle invasion (SVI) which corresponds to stage T3b (see Section 5.2 for details).

5.3.1.2 DRE, PSA level and biopsy findings

The first level of assessment is local tumour stage because the distinction between organ-confined (T1/T2) and extraprostatic (T3/T4) disease affects treatment decisions. Digital rectal examination is positively correlated with tumour stage in $< 50\%$ of cases [209], although it often underestimates tumour extension. More extensive T-staging is only recommended if it directly affects treatment decisions.

Serum PSA levels increase with tumour stage, although they are limited for accurate prediction of final

pathological stage [210]. In prostate needle biopsy, the percentage of cancerous tissue is a strong predictor of positive surgical margins, SVI, and non-organ-confined disease [211]. An increase in tumour-positive biopsies is an independent predictor of EPE, margin involvement, and lymph node (LN) invasion [212]. Serum PSA, Gleason score, and T-stage are more useful together than alone in predicting final pathological stage [192, 213]. Models may help to select candidates for nerve-sparing surgery and lymphadenectomy LND) (see Section 6.2.5).

Seminal vesicle invasion is predictive of local relapse and distant metastatic failure. Seminal vesicle biopsies can improve pre-operative staging accuracy [214]. This is not recommended for first-line examination, but should be reserved for patients with high risk of SVI in whom a positive biopsy would modify treatment. Patients with T-stage > 2a and serum PSA > 10 ng/mL are candidates for SV biopsy [215, 216]. Patients with positive biopsies from the base of the prostate are more likely to have positive SV biopsies [217].

Transperineal 3D prostate mapping biopsy (PMB) is an alternative to transrectal biopsies because it provides more accurate tumour localisation, extent and Gleason grading [218], and has acceptable morbidity [147].

5.3.1.3 *Transrectal ultrasound*

Transrectal ultrasound is no more accurate at predicting organ-confined disease than DRE [219]. Transrectal ultrasound-derived techniques (e.g. 3D-TRUS, colour Doppler) [220, 221] cannot differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine staging.

5.3.1.4 *Multiparametric magnetic resonance imaging*

T2-weighted imaging remains the most useful method for local staging on mpMRI. At 1.5T (Tesla), mpMRI has good specificity but low sensitivity for detecting T3 stages. Pooled data from a meta-analysis for EPE, SVI, and overall stage T3 showed a sensitivity and specificity of 0.57 (95% CI: 0.49-0.64) and 0.91 (95% CI: 0.88-0.93), 0.58 (95% CI: 0.47-0.68) and 0.96 (95% CI: 0.95-0.97), and 0.61 (95% CI: 0.54-0.67) and 0.88 (95% CI: 0.85-0.91), respectively [222]. Multiparametric magnetic resonance imaging cannot detect microscopic EPE. Its sensitivity increases with the radius of extension within peri-prostatic fat. In one study, the EPE detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [223]. In another study, mpMRI sensitivity, specificity and accuracy for detecting pT3 stage was, 40%, 95% and 76%, respectively, for focal (i.e. microscopic) EPE, and 62%, 95% and 88% for extensive EPE [224].

The use of high field (3T) or functional imaging in addition to T2-weighted imaging improves sensitivity for EPE or SVI detection [222], but the experience of the reader remains of paramount importance [225] and the inter-reader agreement remains moderate with kappa values ranging from 0.41 to 0.68 [226]. Multiparametric magnetic resonance imaging, although not perfect for local staging, may improve prediction of the pathological stage when combined with clinical data [227, 228]. Other MRI-derived parameters such as the tumour volume or the contact length of the tumour with the capsule [229-231], or the Gleason score obtained through MRI-TBx [232] could further improve the local staging.

Given its low sensitivity for focal (microscopic) EPE, mpMRI is not recommended for local staging in low-risk patients [227, 233, 234]. However, mpMRI can still be useful for treatment planning in selected low-risk patients (e.g. candidates for brachytherapy) [235].

5.3.2 *N-staging*

N-staging should be performed only when it might directly influence treatment decisions. High PSA values, T2b-T3 stage, poor tumour differentiation and perineural invasion are associated with high risk of nodal metastases [236, 237]. Measurement of PSA alone is unhelpful in predicting LN metastases. Nomograms can define patients at low risk (< 10%) of nodal metastasis, although nomograms may be more accurate in establishing the extent of nodal involvement [213, 238]. The simple Roach formula can also be used [239]. Patients with low- and intermediate-risk PCa may be spared N-staging before potentially curative treatment.

Gleason 4 pattern in sextant biopsies can define the risk of N1 disease. Risk of nodal metastases was 20-45% if any core had a predominant Gleason 4 pattern, or > 3 cores had any Gleason 4 pattern. For the remaining patients, the risk was 2.5%, suggesting that nodal staging is unnecessary in selected patients [240].

5.3.2.1 *Computed tomography and magnetic resonance imaging*

Abdominal CT and T1-T2-weighted MRI indirectly assess nodal invasion by using LN diameter and morphology. However, the size of non-metastatic LNs varies widely and may overlap with the size of LN metastases, since microscopic invasion does not enlarge LNs. The normal range for non-metastatic LNs also varies with different anatomical regions. As a result, the ideal size threshold remains unclear [241, 242]. Computed tomography and MRI sensitivity is less than 40% [243, 244]. Among 4,264 patients 654 (15.3%) of

whom had positive LNs at LND, CT was positive in only 105 (2.5%) patients [241]. Detection of microscopic LN invasion by CT is < 1% in patients with a Gleason score < 8, PSA < 20 ng/mL, or localised disease [245-247].

Diffusion-weighted MRI may detect metastases in normal-sized nodes, but a negative diffusion-weighted MRI cannot rule out the presence of LN metastases [242, 248]. Moreover, this scan is technically challenging to perform in the pelvis where artifacts due to bowel gas can interfere with the quality of the imaging.

Because of their low sensitivity, CT or MRI should not be used for nodal staging in low-risk patients and be reserved for high-risk cancer patients.

5.3.2.2 Choline PET/CT

^{11}C - or ^{18}F -choline positron emission tomography (PET)/CT have good specificity for LN metastases, but a sensitivity of 10-73% [249, 250].

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases were 62% (95% CI: 51-66%) and 92% (95% CI: 89-94%), respectively [251]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10-35%), the sensitivity was only 8.2% in a region based and 18.9% at a patient-based analysis, which is too low to be of clinical interest [252].

In intermediate/high-risk patients, comparisons between choline PET/CT and diffusion-weighted MRI gave contradictory results, with PET/CT sensitivity found to be superior [253], similar [254, 255] or inferior [252] than that of diffusion-weighted MRI.

Because of its insufficient sensitivity, choline PET/CT does not reach clinically acceptable diagnostic accuracy for detection of LN metastases.

5.3.2.3 New methods

^{68}Ga -labelled prostate-specific membrane antigen-PET CT (^{68}Ga -PSMA PET/CT) seems to exhibit promising sensitivity for LN involvement. A recent meta-analysis of five retrospective studies, performed in an initial staging and/or recurrence setting, reported combined sensitivities and specificities of 86% (95% CI: 37-98%) and 86% (95% CI: 3-100%) at patient level, and 80% (95% CI: 66-89%) and 97% (95% CI: 92-99%) at lesion level [256]. Similarly, ^{18}F -labelled PSMA targeting compounds are being developed commercially. However, these results must be interpreted with care, as careful validation studies have not been performed.

5.3.3 M-staging

5.3.3.1 Bone scan

$^{99\text{m}}\text{Tc}$ -Bone scan (BS) has been the most widely used method for evaluating bone metastases of PCa. A 2014 meta-analysis showed a combined sensitivity and specificity of 79% (95% CI: 73-83%) and 82% (95% CI: 78-85%) at patient level and 59% (95% CI: 55-63%) and 75% (95% CI: 71-79%) at lesion level [257]. Adding single-photon emission computed tomography (SPECT) to plain BS has been shown to reduce the number of equivocal lesions [258]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour Gleason score and these three factors were the only independent predictors of BS positivity in a study of 853 patients [259]. The mean BS positivity rate in 23 different series was 2.3% in patients with PSA levels < 10 ng/mL, 5.3% in patients with PSA level between 10.1 and 19.9 ng/mL, and 16.2% in patients with PSA levels of 20.0-49.9 ng/mL. It was 6.4% in men with organ-confined cancer and 49.5% in men with locally advanced cancers. Detection rates were 5.6% and 29.9% for Gleason scores of 7 and ≥ 8 respectively [241]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive BS [260, 261].

Bone scanning should be performed in symptomatic patients, independent of PSA level, Gleason score or clinical stage [241].

5.3.3.2 Other modalities

^{18}F -sodium fluoride (^{18}F -NaF) PET or PET/CT shows similar specificity and superior sensitivity to BS. It may even have the highest sensitivity for bone metastases, as compared to all other imaging techniques [262, 263]. However, unlike choline PET/CT, it does not detect LN metastases, and it is less cost-effective compared to BS [262].

It remains unclear whether choline PET/CT is more sensitive than conventional BS, but it has higher specificity, with fewer indeterminate bone lesions [249, 251, 264].

Diffusion-weighted whole-body and axial MRI are more sensitive than BS and targeted conventional radiography in detecting bone metastases in high-risk PCa [265, 266]. Whole-body MRI is also more sensitive and specific than combined BS, targeted radiography and abdominopelvic CT [267]. A meta-analysis found that MRI is more sensitive than choline PET/CT and BS for detecting bone metastases on a per-patient basis, although choline PET/CT had the highest specificity (Table 5.3.1) [257].

Only limited evidence is available on the performance of ^{68}Ga -PSMA PET/CT in initial staging. A meta-analysis reported a combined positivity rate of 40% (95% CI: 19-64%) in patients undergoing primary staging. However, the positivity rate fell to 27% (95% CI: 15-42%) when studies with a sample size < 10 were excluded [256].

Table 5.3.1: Sensitivity and specificity for detecting bone metastases on a per-patient basis [257]

Imaging modality	Sensitivity %	Specificity %	CI
Bone scan	78	85	95% (0.73-0.83)
Choline PET/CT	91	99	95% (0.83-0.96)
MRI	97	95	95% (0.91-0.99)

CI = confidence interval; mpMRI = multiparametric magnetic resonance imaging; PET = positron emission tomography.

Although evidence shows that choline PET/CT and mpMRI are more accurate than BS, the clinical benefit of detecting bone metastases at an earlier time-point using more sensitive techniques remains unclear in the initial staging setting [268]. Bone scan is therefore usually preferred in most centres.

5.4 Guidelines for staging of prostate cancer

Any risk group staging	LE	GR
Do not use computed tomography and transrectal ultrasound for local staging.	2a	A

Low-risk localised PCa	LE	GR
Do not use additional imaging for staging purposes.	2a	A

Intermediate-risk PCa	LE	GR
In predominantly Gleason pattern 4 (ISUP grade 3), include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.	2a	A*
In predominantly Gleason pattern 4 (ISUP grade 3), use prostate multiparametric magnetic resonance imaging (mpMRI) for local staging.	2b	A

*Upgraded following panel consensus.

High-risk localised PCa/High-risk locally advanced PCa	LE	GR
Use prostate mpMRI for local staging.	2b	A
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	A

6. DISEASE MANAGEMENT

6.1 Treatment: Deferred treatment (active surveillance/watchful waiting)

6.1.1 Introduction

Many men with screening-detected localised PCa will not benefit from definitive treatment [269] and 45% of them are candidates for deferred management. There are two distinct strategies for conservative management that aim to reduce over-treatment: active surveillance (AS) and watchful waiting (WW) (Table 6.1.1).

6.1.1.1 Definition

6.1.1.1.1 Active surveillance

Active surveillance aims to achieve correct timing for curative treatment in patients with clinically localised PCa, rather than delay palliative treatment [270]. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening disease, still potentially curable, while considering individual life expectancy.

6.1.1.1.2 Watchful waiting

Watchful waiting (WW) is also known as deferred or symptom-guided treatment. It refers to conservative management, until the development of local or systemic progression with (imminent) disease-related complaints. Patients are then treated according to their symptoms, in order to maintain QoL.

Table 6.1.1: Definitions of active surveillance and watchful waiting [269]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Low-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging.

6.1.2 Deferred treatment of localised PCa (stage T1/T2, Nx/N0, M0)

Mortality from untreated screen-detected PCa in patients with Gleason scores 5-7 might be as low as 7% at fifteen years follow-up [269].

6.1.2.1 Active surveillance

Active surveillance is currently reserved for selected low-risk patients. Current data are from ongoing prospective or retrospective cohorts; no formal RCT is available comparing this modality to standard treatment. The ProtecT trial [271] is discussed later as it is not a formal AS strategy.

One of the largest published cohorts with the longest follow-up in a mainly low-risk population includes 993 patients (mean age: 67.8 years) [272]. These men presented with stage T1c or T2a and PSA ≤ 10 ng/mL, age ≤ 70 years and a Gleason score ≤ 6 or age > 70 years with a Gleason score of ≤ 7 . After a median follow-up of 6.4 years the ten- and fifteen-year OS were 80% and 62%, respectively, and DSS rates were 98.1% and 94.3%, respectively. Twenty-seven percent of this cohort eventually underwent radical treatment, prompted by a PSA-DT < 3 years (43.5%), a Gleason score progression on repeat biopsies (35%) and patient preference (6%). Thirty men (3%) developed metastases during follow-up: 2% of those initially classified as Gleason 6 compared to 9.7% if initially Gleason 7, and fifteen men died [273].

Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a SR including $> 3,900$ patients [274]. There is considerable variation between studies regarding patient selection, follow-up policies and when active treatment should be instigated.

Selection criteria for AS are limited by a lack of prospective RCTs, or findings from a formal consensus meeting. The criteria most often published include: Gleason 6, when specified $< 2-3$ positive cores with $< 50\%$ cancer involvement in every positive core, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc [274, 275]. The latter threshold remains controversial [275, 276]. A pathology consensus group suggested excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure intraductal carcinoma), sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [277] and perineal invasion [278]. A Canadian consensus group pose that AS is the treatment of choice for low-risk disease, without stratifying for biopsy results, although they clearly recommend that men < 55 years should be closely scrutinised for high-volume Gleason 6 cancer. The same authors pose that low volume Gleason 7 (3 + 4) ($< 10\%$ pattern 4) may also be considered for AS. However, recent findings suggest that any grade 4 pattern is associated with a three-fold increased risk of metastases compared to Gleason 6, while a PSA up to 20 ng/mL might be an acceptable threshold [279-281].

In this setting, re-biopsy within six to twelve months to exclude sampling error is mandatory [275, 281] even if this could be modified in the future [282].

Biological markers, including urine PCA3, transmembrane protease, serine 2-TMPRSS2-ERG fusion, or PSA isoforms appear promising, as does genomics on the tissue sample itself [283-285]. However, further data will be needed before such markers can be used in standard clinical practice.

Imaging with mpMRI is of particular interest due to its high NPV value for lesion upgrading and for staging anterior prostate lesions [286, 287]. A formal SR is available [287]. The added value of mpMRI and targeted biopsies could be promising in:

1. reducing misclassifications at initial diagnosis and follow-up;
2. reducing unnecessary (targeted or systematic) biopsies at follow-up, and;
3. aiding in monitoring patients on surveillance.

The added value may differ at different time points in an AS setting. At confirmatory biopsy in men who did not have an mpMRI before, the reclassification rate due to targeted biopsies can be estimated to be 2-22% (absolute numbers) [287-291]. The added value of mpMRI for surveillance/repeat biopsies (hence more than one year following the confirmatory biopsy assessment) has not been evaluated yet. However, combined data of confirmatory and surveillance repeat biopsies show a reclassification rate due to targeted biopsies of 2-14% (absolute numbers) [292-294]. These numbers are directly related to the eligibility criteria for AS, and the reclassification criteria used within these populations.

The concordance of systematic and targeted biopsies at confirmatory biopsies is approximately 80%. However omitting systematic biopsies may induce a misclassification rate of 3-13% [287-290, 292-294], therefore systematic biopsy should be systematically performed, even facing a normal mpMRI.

Targeted biopsies of suspicious lesions on mpMRI are mainly performed for Likert/PIRADS (Prostate Image Reporting and Data System) ≥ 3 lesions. Although increased rates of reclassification occur in PIRADS 4 and 5 lesions, a substantial proportion of PIRADS 3 lesions show reclassification following targeted biopsies [288, 289], thereby confirming the significance to biopsy Likert/PIRADS ≥ 3 lesions within AS management.

The follow up strategy is based on serial DRE (at least once/year), PSA (at least once, every six months) and repeated biopsy (at a minimum interval of three to five years). Based on two small single centre studies [295, 296], not all patients with progression/reclassification at biopsy had radiological progression and vice versa. Therefore, mpMRI cannot be used as a stand-alone tool to trigger follow-up biopsies, but efforts are being made to define and standardise radiological progression during AS [297].

Risk prediction in men on AS is under investigation to further reduce unnecessary biopsies and misclassification [298]. In an AS cohort of 259 men with Gleason 6 and Gleason 7 (3 + 4) cancers detected by MRI-targeted and systematic biopsies, independent predictors of upgrading at 3 years were Gleason 7 (3 + 4), PSA density ≥ 0.15 ng/mL/cm³ and a score 5 lesion on MRI [299]. Thus, the role of mpMRI in risk prediction should be further investigated.

Switching to active treatment

The decision to start active treatment should be based on a change in the biopsy results (Gleason score, number of positive cores, length in the core involvement), or T-stage progression. These criteria are recognised in all published cohorts. A PSA change (especially a PSA-DT < 3 years) is a less powerful indicator to change management based on its weak link with grade progression [300, 301]. Active treatment may also be instigated upon a patient's request. This occurs in around 10% of patients on AS [302]. Overall, no major perturbation of health-related QoL (HRQoL) and psychological well-being was apparent in the first years [303].

Table 6.1.2: Active surveillance in screening-detected prostate cancer

Studies	n	Median follow-up (mo)	pT3 in RP patients*	OS	CSS
Van As <i>et al.</i> , 2008 [304]	326	22	8/18 (44%)	98	100
Carter <i>et al.</i> , 2007 [305]	407	41	10/49 (20%)	98	100
Adamy <i>et al.</i> , 2011 [306]	533-1,000	48	4/24 (17%)	90	99
Soloway <i>et al.</i> , 2010 [307]	99	45	0/2	100	100
Roemeling <i>et al.</i> , 2007 [308]	278	41		89	100
Khatami <i>et al.</i> , 2007 [309]	270	63		n.r.	100
Klotz <i>et al.</i> , 2015 [272]	993	77	n.r.	85	98.1
Total	2,130-3,000	43		90	99.7

* Patients receiving active therapy following initial active surveillance.

CSS = cancer-specific survival; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.

6.1.2.2 Watchful waiting

The rationale behind WW is that PCa often progresses slowly, and is predominantly diagnosed in older men with a high incidence of comorbidity and other causes of mortality [310]. Watchful waiting is possible in patients with localised PCa and a limited life expectancy.

6.1.2.2.1 Patient selection for watchful waiting

Studies on WW have included patients with up to 25 years of follow-up, with endpoints of OS and CSS. Several series have shown a consistent CSS rate of 82-87% at ten years [311-316], and 80-95% for T1/T2 and Gleason score ≤ 7 [317]. In three studies with data beyond fifteen years, the DSS was 80%, 79% and 58% [313, 315, 316], and two reported twenty-year CSS rates of 57% and 32%, respectively [313, 315]. Many patients classified as Gleason 6 would now be classified as Gleason 7 based on the revised Gleason classification, suggesting that the above-mentioned results should be considered as minimal. Patients with well-, moderately- and poorly-differentiated tumours had ten-year CSS rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis [317]. Observation was most effective in men aged 65-75 years with low-risk PCa [318].

Gleason 6-10 tumours carry a continuously increasing mortality risk up to fifteen years follow-up after WW [319]. Others have shown that the mortality risk of PCa was high in Gleason 7-10 tumours, intermediate in Gleason 6 tumours, but low in Gleason 2-5 tumours (Table 6.1.3) [320, 321].

In an analysis at ten years follow up in 19,639 patients aged > 65 years who were not given curative treatment, most men with a Charlson comorbidity index (CCI) score ≥ 2 died from competing causes at ten years whatever their initial age. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score ≤ 1 had a low risk of death at ten years, especially for well- or moderately-differentiated lesions [322]. This highlights the importance of checking the CCI before considering a biopsy.

Table 6.1.3: Fifteen-year mortality risk for localised PCa in relation to Gleason score in patients aged 55-74 years [320, 321, 323]

Gleason score	Cancer mortality risk* (%)	Cancer-specific mortality† (%)
2-4	4-7	8
5	6-11	14
6	18-30	44
7	42-70	76
8-10	60-87	93

* Figures differ among age groups and represent the true risk in the study population (considering actual competing mortality from other causes).

† Figures compensate for differences in competing mortality and indicate outcome if the patient lives for fifteen years.

6.1.2.2.2 Outcome of watchful waiting compared to active treatment

The SPCG-4 randomised study compared WW to RP (Table 6.1.4) [323] before the PSA era and found RP to provide superior CSS, OS and progression-free survival (PFS) compared to WW at a median follow-up of 12.8 years. The PIVOT trial made a similar comparison in 731 randomised men (50% with non-palpable disease) [324] and found no benefit of treatment within ten years. Only patients with serum PSA > 10 ng/mL or high-risk PCa had a significant OS benefit from RP, with a relative-risk reduction in mortality of 33% and 31%, respectively. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%). Overall, no major perturbation of HRQoL and psychological well-being was apparent in the first years [325].

Table 6.1.4: Outcome of SPCG-4 at fifteen years follow-up [323]

	RP (n = 348) (%)	Watchful waiting (n = 348) (%)	Relative risk (95% CI)	p-value
Disease-specific mortality	14.6	20.7	0.62	0.010
Overall mortality	46.1	57.2	0.75 (0.61-0.92)	0.007
Metastatic progression	21.7	33.4	0.59 (0.45-0.79)	< 0.001
Local progression	21.5	49.3	0.34 (0.26-0.45)	n.r.

CI = confidence interval; n.r. = not reported; RP = radical prostatectomy.

The data on deferred and conservative management of low-risk disease contrasts with the recent increase in the incidence of local treatment from 25 to 34% in the USA in men with a life expectancy < 10 years [326]. Swedish data show a higher prevalence of deferred treatment in low-risk disease of 46% [327].

6.1.2.3 The ProtecT study

The ProtecT trial randomised 1,643 patients between active treatment (RP or EBRT) and active monitoring (AM) [271]. In this AM schedule, patients with a PSA rise of more than 50% in twelve months underwent a repeat biopsy, but none had systematic repeat biopsies (which presents an intermediary approach, between AS and WW). Most patients had low-risk disease with 90% PSA < 10 ng/mL, 77% Gleason 6 (20% Gleason 7), 76% T1c. After ten years of follow up, the CSS was the same between those actively treated and those on AM (99% and 98.8% respectively), as was the OS. Only metastatic progression differed (6% in the AM group as compared to 2.6% in the treated group). The key finding is that AM is as effective as active treatment at ten years, at a cost of increased progression and a double metastatic risk. Metastases remain quite rare (6%), but more frequent compared to results from AS protocols based on patient selection. This confirms that for low-risk patients, some form of initial AM is safe. Beyond ten years, no data is available yet and AS is possibly safer, especially in younger men, based on initial patient selection. Individual life expectancy must be evaluated before considering any active treatment in low-risk situations, and for those with up to ten years individual life expectancy, AM or WW are probably very good options.

6.1.3 Deferred treatment for locally advanced PCa (stage T3-T4, Nx-N0, M0)

The final analysis of the largest RCT focusing on this specific question was published in 2013 [328]. Nine hundred and eighty-five patients with T0-4 N0-2 M0 PCa were treated with androgen-deprivation therapy (ADT), either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS HR was 1.21 (95% CI: 1.05-1.39), favouring immediate treatment but showing no significant difference in PCa mortality or symptom-free survival which raises the question of its clinical value. Patients with a baseline PSA > 50 ng/mL had a > 3.5-fold higher mortality risk than those with a PSA baseline of ≤ 8 ng/mL. If baseline PSA was 8-50 ng/mL, the mortality risk was ~7.5-fold higher in patients with a PSA-DT of < 12 months compared with > 12 months. The median time to start deferred treatment was seven years. In the deferred arm, 25.6% died without needing treatment (44%).

6.1.4 Deferred treatment for metastatic PCa (stage M1)

The only candidates with metastasised disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. Median survival is 42 months, therefore, the time without treatment (before symptoms) is short in most cases. The risk of developing symptoms, and even death from PCa, without receiving any benefit from hormone treatment has been highlighted [329, 330]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

6.1.5 Guidelines for active surveillance and watchful waiting

Recommendations - active surveillance	LE	GR
Discuss surgery and radiotherapy as treatment options with patients suitable for such treatments.	1a	A
Offer active surveillance to patients with the lowest risk of cancer progression: > ten years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	2a	A
Counsel patients about the possibility of needing further treatment in the future.	2a	A
Perform multiparametric magnetic resonance imaging before a confirmatory biopsy.	2b	B
During confirmatory biopsy include systematic and targeted biopsies.	2a	B
Base follow up on digital rectal examination, prostate-specific antigen (PSA) and repeated biopsies.	2a	A

Recommendations - watchful waiting for localised prostate cancer	LE	GR
Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.	1b	A
While on watchful waiting, base the decision to start non-curative treatment on symptoms and disease progression (see Section 6.1.2.2).		B

Recommendations - watchful waiting for locally advanced prostate cancer	LE	GR
In locally advanced M0 patients unwilling or unable to receive any form of local treatment, offer a deferred treatment policy using androgen-deprivation therapy as monotherapy to asymptomatic patients with a PSA doubling time > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.	1b	A

6.2 Treatment: Radical prostatectomy

6.2.1 Introduction

The goal of RP by any approach must be eradication of disease, while preserving continence and, whenever possible, potency [331]. Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes [322]. An estimation of life expectancy is paramount in counselling a patient about surgery [332] (see also Section 6.7). Currently, three large prospective RCTs have reported the benefit of RP over WW [324, 333] and over AM [271] in men with low- and intermediate-risk PCa.

Radical prostatectomy can be performed by open, laparoscopic or robot-assisted (RARP) approach. In a randomised phase III trial, RARP was shown to have reduced admission times and blood loss but not early (twelve weeks) functional or oncological outcomes [334, 335]. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, adjusted for the characteristics of the cancer being treated, can improve cancer control with RP [336-338].

Management decisions should be made after all treatments have been discussed in a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after balancing benefits and side effects of each therapy modality, together with the patient.

6.2.2 Low-risk PCa

At ten years' follow-up, a benefit for metastases-free and PFS but not CSS or OS for RP compared to AM was seen in the ProtecT study where the majority of men had early, localised disease (i.e. > 75% had either clinical T1 or Gleason sum score 6 disease) [271]. In the SPCG-4 study [333], death from any cause and distant metastases was significantly reduced in low-risk PCa at eighteen years of follow up for RP compared with WW, although this finding was based on a sub-group analysis as the majority of men in the trial (i.e. 62%) did not have low-risk disease. However, death from PCa was not reduced. In the PIVOT trial, a pre-planned subgroup analysis of men with low-risk PCa showed that RP did not significantly reduce all-cause mortality or death from PCa at ten years compared with WW.

The decision to offer RP in cases of low-risk cancer should be based on the probability of clinical progression, side-effects and potential benefit to survival [339]. The results of the ProtecT trial suggest that AM and surgery are alternatives to EBRT in patients whose tumours are most likely to be clinically insignificant (this is covered in more detail in Sections 6.1 and 6.3). Apart from disease characteristics, age and comorbidities also impact

on decision-making regarding treatment choices. Individual patient preferences should always be considered in shared decision-making.

If RP is performed in low-risk PCa, pelvic LND is not necessary as the risk for pN+ does not exceed 5% [340].

6.2.3 Intermediate-risk, localised PCa

Patients with intermediate-risk PCa should be informed about the results of two RCTs [324, 333] comparing RP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71; 95% CI: 0.53-0.95), death from PCa (RR: 0.38; 95% CI: 0.23-0.62) and distant metastases (RR: 0.49; 95% CI: 0.32-0.74) were significantly reduced in intermediate-risk PCa at eighteen years. In the PIVOT trial, according to a pre-planned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR: 0.69; 95% CI: 0.49-0.98), but not death from PCa (0.50; 95% CI: 0.21-1.21) at ten years.

When managed with non-curative intent, intermediate-risk PCa is associated with ten- and fifteen-year PCa-specific mortality (PCSM) rates of 13% and 19.6%, respectively [341].

The risk of having positive LNs in intermediate-risk PCa is between 3.7% and 20.1% [340]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [340]. In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes. Table 6.2.1 presents data from three RCTs.

Table 6.2.1: Oncological results of radical prostatectomy in organ-confined disease

Study	Trial	Population	Year of treatment	Median follow-up (mo)	Risk category	12-year CSS (%)	18-year CSS (%)
Bill-Axelsson, <i>et al.</i> 2014 [333]	SPCG-4	Pre-PSA era	1989-1999	160	Low-risk Intermediate-risk		89.8** 84.9**
Wilt, <i>et al.</i> 2012 [324]	PIVOT	Early years of PSA testing	1994-2002	120	Low-risk Intermediate-risk	100** 94.2**	n.a
Hamdy, <i>et al.</i> 2016 [271]	ProtecT	Case-finding	1999-2009	120	Low and intermediate-risk	99.0*	n.a

*10-year CSS

** Based on sub-group analysis of risk groups

CSS = cancer-specific survival; n = number of patients; n.r. = not reported; PSA = prostate-specific antigen; RP = radical prostatectomy.

6.2.4 High-risk and locally advanced PCa

Patients with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP [342]. When managed with non-curative intent, high-risk PCa is associated with ten- and fifteen-year PCSM rates of 28.8% and 35.5%, respectively [341].

There is no consensus regarding the optimal treatment of men with high-risk PCa. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, RP is a reasonable first step in selected patients with a low tumour volume. Extended LND should be performed in all high-risk PCa cases, as the estimated risk for positive LNs is 15-40% [340].

6.2.4.1 High-risk PCa

6.2.4.1.1 Gleason score 8-10

The incidence of organ-confined disease is 26-31% in men with a Gleason 8-10 on biopsy. A high rate of downgrading exists between the biopsy Gleason score and the Gleason score of the resected specimen [343]. Several retrospective case series have demonstrated CSS rates over 60% at fifteen years after RP in the context of a multimodal approach (adjuvant or salvage ADT and/or RT) for patients with a biopsy GS > 8 [343-346] [347].

6.2.4.1.2 Prostate-specific antigen > 20 ng/mL

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multimodal approach demonstrated a CSS at fifteen years of over 70% [345, 346, 348-351].

6.2.4.2 *Locally advanced PCa*

Surgery for locally advanced disease as part of a multimodal therapy has been reported [352-354]. Retrospective case series demonstrated over 60% CSS at fifteen years and over 75% OS at ten years [352-359].

For cT3b-T4 disease, PCa cohort studies showed a ten-year CSS of over 87% and an OS of 65% [360-362].

The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement. Only limited evidence exists supporting RP of cN+ patients. In a recent study, the outcomes of 50 patients with cN+ were compared with those of 252 patients with pN1, but cN0 at pre-operative staging, and cN+ was not a significant predictor of CSS [363].

6.2.5 **Indication and extent of pelvic lymph node dissection**

A recent SR did not show any benefit of performing any PLND during RP for any oncological outcome, including survival [4]. However, it is generally accepted that eLND provides important information for staging and prognosis which cannot be matched by any other currently available procedure [255]. The individual risk of identifying positive LNs can be estimated using pre-operative nomograms. Only a few of these nomograms are based on eLND templates. A risk of nodal metastases over 5% (Briganti nomogram, MSKCC, or Roach formula) is an indication to perform nodal sampling by an eLND [340, 364, 365].

6.2.5.1 *Technique of lymph node dissection*

Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. With this template, 94% of patients are correctly staged [366].

6.2.5.1.1 Sentinel node biopsy analysis

Sentinel node biopsy (SNB) was shown to have a sensitivity of 95.2% for detecting metastases at eLND in a SR [367]. Due to lack of any reliable evidence regarding oncological effectiveness, SNB is still an experimental nodal staging procedure (see Section 5.3.2.3). In addition, controversy regarding definitions and thresholds has limited its application in clinical practice, although efforts to standardise definitions based on consensus have recently been attempted [368].

6.2.6 **Radical prostatectomy in cN0 patients who are found to have pathologically confirmed lymph node invasion (pN1)**

At fifteen years of follow up, cN0 patients who were treated with RP but were found to have pN1 at the time of surgery, were reported to have a CSS and OS of 45% and 42%, respectively [369-375].

In terms of performing frozen section of nodes during RP, two retrospective observational studies have shown a better CSS and OS in favour of a completed RP vs. an abandoned RP in patients who were found to be pN+ at the time of surgery [372, 373, 376]. This highlights the fact that frozen section should no longer be performed and supports the role of RP as an important component of multimodal strategies of pN+ PCa.

6.2.6.1 *Outcome of pN1 disease*

6.2.6.1.1 Prognostic indicators

The number of positive LNs [377], the number of removed LNs [369, 374, 377-382], tumour volume within the LN, and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [383]. A LN density (defined as the percentage of positive LNs in relation to the total number of analysed/removed LNs) over 20% was found to be associated with poor prognosis [384].

6.2.7 **Adjuvant treatment**

6.2.7.1 *Adjuvant treatment after RP*

For patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL, both adjuvant or salvage radiotherapy to the prostatic fossa can be offered. (see Section 6.3.6). Adjuvant androgen ablation with bicalutamide did not improve PFS in localised disease after RP [385]. A SR showed a possible benefit for PFS but not OS for adjuvant androgen ablation therapy [386].

6.2.7.2 *Adjuvant androgen ablation in men with pN1 disease*

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a ten-year CSS rate of 80% [370, 371]. In patients who prove to be pN+ after RP, early adjuvant HT has been shown to significantly improve CSS and OS in a prospective RCT [371]. However, this trial included mostly patients with high-volume

nodal disease and multiple adverse tumour characteristics and the findings may not apply to men with less extensive nodal metastases.

6.2.7.3 Adjuvant radiotherapy in men with pN1 disease

In a retrospective multicentre cohort study, maximal local control with RT of the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated adjuvantly with continuous ADT [375]. However, the beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (< 3 LNs) and GS 7-10 and pT3-4 or R1, as well as men with three to four positive nodes were more likely to benefit from RT after surgery, while the other subgroups did not [375]. In a Surveillance, Epidemiology and End Results (SEER) retrospective population-based analysis, adding RT to RP showed a non-significant trend for improved OS but not PCa-specific survival, but data on the extent of additional RT is lacking in this study [376]. No recommendation can be made for the extent of adjuvant RT in pN1 disease although whole pelvis RT was given in more than 70% of men in a large retrospective series which identified a benefit for adding RT to androgen ablation in pN1 patients [375]. However the optimal field (prostatic fossa only or whole pelvis) remains unclear.

6.2.7.4 Adjuvant chemotherapy

The TAX3501 trial, compared the role of leuprolide (eighteen months) with, and without, docetaxel (six cycles) closed prematurely due to poor accrual [387]. Adjuvant chemotherapy after RP should only be considered within a clinical trial.

6.2.7.5 Guidelines for extended lymph node dissection in prostate cancer and pN+ patients

Recommendations	LE	GR
Do not perform a lymph node dissection (LND) in low-risk PCa.	2b	A
Perform an extended(e)LND in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5%.	2b	B
Perform an eLND in high-risk PCa.	2a	A
Do not perform a frozen section of nodes during radical prostatectomy (RP) to decide whether to proceed with, or abandon, the procedure.	2a	A
Do not perform a limited LND.	2a	A
Upon detection of nodal involvement during RP:		
• offer adjuvant androgen deprivation therapy (ADT);	1b	A
• discuss adjuvant ADT with additional radiotherapy (see Section 6.2.6.3);	2b	A
• offer observation (expectant management) to a patient after eLND with < 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	2b	B

6.2.8 Comparing RP surgical approaches

A previous SR and meta-analysis of non-RCTs demonstrated that RARP had lower peri-operative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy (LRP), although there was considerable methodological uncertainty [388]. There was no evidence of differences in urinary incontinence (UI) rates at twelve months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or erectile dysfunction (ED) outcomes. There is a lack of studies comparing the different surgical modalities for these longer-term outcomes [388-394]. Another SR and meta-analysis [335] included two small RCTs comparing RARP vs. LRP. The results suggested higher rates of erectile function recovery (RR 1.51; 95% CI: 1.19-1.92) and restoring early continence (RR 1.14; 95% CI: 1.04-1.24) in the RARP group. Increased surgical experience has lowered the complication rates of RP and improved cancer cure [395-398]. Consequently, there is emerging data to suggest some benefits of the robotic approach over the laparoscopic and open approaches, in terms of perioperative, recovery and short-term functional outcomes; however, there is uncertainty over oncological outcomes, longer-term functional and QoL outcomes [334].

6.2.9 Indications for nerve-sparing surgery

Nerve-sparing RP can be performed safely in most men with localised PCa [399, 400]. Clear contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT2c or cT3 PCa, and any GS > 7 on biopsy. An externally validated nomogram predicting side-specific extracapsular extension can help guide decision making [401, 402]. Multiparametric MRI might be helpful in selecting a nerve-sparing approach (see Section 5.3.1.4).

If any doubt remains regarding residual tumour, the surgeon should remove the neurovascular bundle (NVB). Alternatively, the use of intra-operative frozen-section analysis can help guide these decisions [403].

There is conflicting data on the early use of phosphodiesterase-5 (PDE5) inhibitors in penile rehabilitation post-surgery [404, 405]. However, a large multicentre RCT including men < 68 years old with normal pre-operative erectile function, showed benefit from daily dosing of 5 mg tadalafil, after nerve-sparing RP for organ-confined non-metastatic PCa [406].

6.2.10 Guidelines for radical prostatectomy

Recommendations	LE	GR
Offer both radical prostatectomy (RP) and RT in patients with low- and intermediate-risk disease and a life expectancy > 10 years.	1b	A
Offer AS as an alternative to surgery or RT in patients with low-risk disease and a life expectancy of > 10 years.	1b	A
Offer nerve-sparing surgery in patients with a low risk of extracapsular disease (refer to Partin tables/nomograms).	2b	B
Offer RP in patients with high-risk localised PCa and a life expectancy of > 10 years only as part of multi-modal therapy.	2a	A
Offer RP in selected patients with locally advanced (cT3a) disease and a life expectancy > 10 years only as part of multi-modal therapy.	2b	B
Offer RP in highly selected patients with locally advanced disease (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.	3	C
Do not offer neoadjuvant hormonal therapy before RP.	1a	A
Do not offer adjuvant hormonal therapy after RP for pN0 disease.	1a	A

6.3 Treatment: definitive radiotherapy

6.3.1 Introduction

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the accepted best standard for EBRT. Regardless of the technique used, the choice of treatment is multidisciplinary. After the extent of the tumour has been properly assessed, the following are taken into account [407]:

- 2017 TNM classification;
- gleason score, defined using an adequate number of core biopsies (at least 10);
- baseline PSA;
- age of the patient;
- patient's comorbidity, life expectancy, and QoL;
- International Prostate Symptom Score (IPSS) and uroflowmetry recordings (max urinary peak flow > 15 mL/s when considering brachytherapy [408]);
- and the EAU prognostic factors classification.

6.3.2 Technical aspects: three-dimensional conformal radiotherapy and intensity-modulated external-beam radiotherapy

Anatomical data are acquired by scanning the patient in the treatment position. The data are transferred to the three-dimensional (3D) treatment planning system, which visualises the clinical target volume and then adds a surrounding safety margin. Real-time verification of the irradiation field using portal imaging allows comparison of the treated and simulated fields, and correction of deviations where displacement is more than 5 mm.

It is possible to use IMRT with linear accelerators, equipped with the latest multileaf collimators and specific software. At the time of irradiation, a multileaf collimator automatically (and in the case of IMRT continuously) adapts to the contours of the target volume seen by each beam. This allows for a more complex distribution of the dose to be delivered within the treatment field and provides concave isodose curves, which are particularly useful as a means of sparing the rectum. To date, no RCT have been published comparing dose escalation using IMRT and 3D-CRT.

With dose escalation using IMRT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of IGRT, in which organ movement can be visualised and corrected for in real time, although the optimum means of achieving this is still unclear [409]. Tomotherapy is another evolving technique for the delivery of IMRT, which uses a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning.

Whatever the techniques and their degree of sophistication, quality assurance plays a major role in the management of RT, requiring the involvement of physicians, physicists, dosimetrists, radiographers, radiologists and computer scientists.

6.3.3 Radiotherapy for localised PCa

6.3.3.1 Dose escalation

Several RCTs have shown that dose escalation (range 74-80 Gy) has a significant impact on five-year survival without biochemical relapse [410-419]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant HT has varied. The best evidence of an OS benefit for patients with intermediate- or high-risk PCa, but not with low-risk PCa, comes from a non-randomised but well conducted propensity-matched retrospective analysis of the U.S. National Cancer Database (NCDB) covering a total of 42,481 patients [420].

In everyday practice, a minimum dose of ≥ 74 Gy is recommended for EBRT + HT.

Currently, it is not possible to make different recommendations according to the patient's risk group.

If IMRT and IGRT are used for dose escalation, severe late side effects \geq Grade 3 for the rectum is about 2-3% and for the genito-urinary tract is 2-5% [412, 419, 421-434] (see also Chapter 8).

Table 6.3.1: Randomised trials on dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up	Outcome	Results
MD Anderson 2011 [410]	301	T1-T3, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	70 vs. 78 Gy	Median 9 yr	Disease specific mortality (DSM) vs. other cause of death	High risk/PSA > 10 16 % DSM @ 70 Gy 4% DSM @ 78 Gy ($p = 0.05$) Higher risk 15% DSM @ 70 Gy 2% DSM @ 78 Gy ($p = 0.03$)
PROG 95-09 2010 [411]	393	T1b-T2b PSA 15 ng/mL 75% GS < 6	70.2 vs. 79.2 Gy including proton boost 19.8 vs. 28.8 Gy	Median 8.9 yr. for survivors	10-year ASTRO BCF	All patients: 32% BF @ 70.2 Gy 17% BF @ 79.2 Gy ($p < 0.0001$) Low-risk patients: 28% BF @ 70.2 Gy 7% BF @ 79.2 Gy ($p < 0.0001$)
MRC RT01 2014 [407]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	Median 10 yr.	BFS; OS	43% BFS @ 64 Gy 55% BFS @ 74 Gy ($p = 0.0003$) 71% OS both groups ($p = 0.96$)
Dutch RCT 2014 [419]	664	T1b-T4 143 pts. with (neo)adjuvant HT	68 vs. 78 Gy	Median 110 mo.	Freedom biochemical (Phoenix) and/or clinical failure (FFF) @ 10 yr.	43% FFF @ 68 Gy 49% FFF @ 78 Gy ($p = 0.045$)
French GETUG 06 2011 [414]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	Median 61 mo.	BCF (ASTRO)	39% BF @ 70 Gy 28% BF @ 80 Gy
Retrospective NCDB study 2015 [420]	16,714	intermediate risk 73% T \leq 2a 76% GS \leq 7a	< 75.6 Gy vs. \geq 75.6 Gy 49% HT	Median 85-86 mo.	OS	Propensity adjusted HR: 0.84 favouring dose escalation ($p < 0.001$)
	13,538	high risk 40% T \geq 2b 67% GS \geq 7b	< 75.6 Gy vs. \geq 75.6 Gy 77% HT			Propensity adjusted HR: 0.82 favouring dose escalation ($p < 0.001$)

BCF = biochemical failure; BFS = biochemical progression-free survival; GS = Gleason score; HR = hazard ratio; HT = hormone therapy; OS = overall survival; PSA = prostate-specific antigen.

6.3.3.2 Hypofractionation

In radiobiology, the linear quadratic model uses two coefficients, alpha (α) and beta (β) to describe the dose-response relationship. In clinical practice, these coefficients are used to calculate the effect of different fractionation schemes. Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue. In fast growing tissue including many tumours, cells have little time to repair photon-induced DNA damage. The α/β ratio is then typically around 10 Gy. In contrast, tissue with a low cell renewal has a good opportunity for repair between fractions of irradiation. In such tissue, the α/β ratio is 3 Gy or lower. Slowly proliferating cells with low α/β ratios are very sensitive to an increased dose per fraction [417].

While the correct α/β ratio is still controversial, a meta-analysis of 25 studies with > 14,000 patients concludes that PCa, due to its slow growth, has an α/β ratio of approximately 1.5 Gy. Assuming this value, hypofractionated RT could be more effective than conventional fractions of 1.8-2 Gy [418]. Beyond the radiobiological aspects, hypofractionation (HFX) can increase the convenience for the patient and lower costs for the health care system.

Several studies report on HFX applied in various techniques and in part also including HT [435-444]. A SR concludes that studies on moderate HFX (2.5-4 Gy/fx) delivered with conventional 3D-CRT/IMRT have sufficient follow-up to support the safety of this therapy, but long-term efficacy data are still lacking [445]. Extreme HFX (5-10 Gy/fx) typically requires IGRT and stereotactic body radiotherapy (SBRT). Short-term biochemical control is comparable to conventional fractionation. However, there are concerns about high-grade genitourinary and rectal toxicity, and long-term side effects may not all be known yet [445-447].

On behalf of the German Society of Radiation Oncology, an international expert panel has released a comprehensive overview on HFX for clinical routine [448]. Taking into account the published results and the uncertainties of the correct α/β ratio, moderate HFX (Table 6.3.2) plus dose escalation should be done by experienced teams, accompanied by meticulous RT quality assessment and close attention to organ-at-risk dose-constraints until long-term data are available. It should be restricted to high-quality EBRT using IGRT and IMRT in carefully selected patients and adhere to published phase 3 protocols with documented safety and efficacy. The Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHiP)-regimen with 60 Gy in 20 fractions over four weeks or the RTOG regimen with 70 Gy in 28 fractions over six weeks at present seem to be the first choices. Meticulous follow-up and documentation of outcome and late toxicity are mandatory. Hypofractionation to the pelvic LNs and post-operative HFX in the adjuvant or salvage setting are experimental and should be reserved for clinical trials.

Table 6.3.2: Major phase 3 randomised trials of moderate hypofractionation for localised PCa

Study	n	Risk, GS, or NCCN	Regimen	BED, Gy	Median FU, mo	Outcome	Toxicity
Lee <i>et al.</i> 2016 [439]	550 542	low risk	70 Gy/28 fx 73.8 Gy/41 fx	80 69.6	70	5 yr. DFS 86.3% (NS) 5 yr. DFS 85.3 %	Gr 2 GI 18.3% (p = 0.005) Gr 2 GU 26.2% (p = 0.009) Gr 2 GI 11.4% Gr 2 GU 20.5%
Dearnaley <i>et al.</i> 2012, 2016 [435, 440]	1077/19 fx 1074/20 fx 1065/37 fx	15% low 73% intermediate 12% high	57 Gy/19 fx 60 Gy/20 fx 74 Gy/37 fx	73.3 77.1 74	62	5 yr. BCDF 85.9% (19 fx) 90.6% (20 fx) 88.3% (37 fx)	acute Gr ≥ 2 GI 38% (19 fx) 38% (20 fx) 25% (37 fx) 5 yr. Gr ≥ 2 GI 11.3% (19 fx) 11.9% (20 fx) 13.7 (37 fx) 5 yr. Gr ≥ 2 GU 6.6% (19 fx) 11.7% (20 fx) 9.1% (37 fx)
Aluwini <i>et al.</i> 2015, 2016 [438, 443, 444]	403 392	30% GS < 6 45% GS > 7 25% GS 8-10	64.6 Gy/19 fx 78 Gy/39 fx	90.4 78	60	5 yr. RFS 80.5% (NS) 5 yr. RFS 77.1%	3 yr. Gr ≥ 2 GU 41.3% Gr ≥ 3 GU 19.0% (p = 0.02) Gr ≥ 2 GI 21.9% 3 yr. Gr ≥ 2 GU 39.0% Gr ≥ 3 GU 12.9% Gr ≥ 2 GI 17.7%

BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/β of 1.5 Gy; DFS=disease-free survival; FU = follow-up; fx = fractions; GI = gastrointestinal; Gr = Grade; GS = Gleason score; GU = genito-urinary; NCCN = National Comprehensive Cancer Network; NS = not significant; n.s.= not stated.

Radiotherapy with > 3.4 Gy has been suggested to define extreme HFX [448]. Respective studies largely include low- to intermediate-risk patients and obtain very favourable results. Table 6.3.3 gives an overview on selected studies. It seems prudent to restrict extreme HFX to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Table 6.3.3: Selected trials on extreme hypofractionation for localised PCa

Reference	n	med FU (mo.)	Risk-Group	Techniques	Regimen (TD/fx)	Outcome	Toxicity
Freeman <i>et al.</i> 2014 [449]	1,743	n.s.	41% low 42% intermediate 10% high 7% data missing	mainly robotic IGRT	35-40 Gy/4-5 fx (8% SBRT-boost 19.5-21.8 Gy/3 fx after 45-50 Gy EBRT)	FFBF 92% @ 2 yr. 99% low risk 97-85% interm. risk 87% high risk	G3 GU 0% G3 GI 0%
Katz <i>et al.</i> 2014 [450]	515	72	63% low 30% intermediate 7% high	robotic IGRT	35-36.25 Gy/5 fx	FFBF @ 7yr. 96% low risk 89% interm.risk 69% high risk	G ≥ 2 GU 9% G ≥ 2 GI 4%

FFBF = freedom from biochemical failure; FU = follow-up; TD = total dose; fx = number fractions; GI = gastrointestinal; G = grade; GU = genitourinary; IGRT = image-guided radiation therapy; n.s. = not stated; EBRT external beam radiotherapy in standard fractionation.

6.3.3.3 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of RT with luteinising-hormone-releasing hormone (LHRH) ADT has definitively proven its superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [451-455] (Table 6.3.3). These trials included high-risk PCa patients, mostly by virtue of locally advanced (T3-T4 N0-X) disease, though with a wide range of clinical risk factors, such as PSA level or Gleason grade (high-risk localised, T1-2, N0-X PCa). The most powerful conclusion from these studies comes from the EORTC 22863 trial, which is the basis for the combination of RT and ADT in patients with locally advanced PCa as standard practice today.

In daily practice, ADT starts either at the onset of RT (for adjuvant ADT) or two or three months before (for neoadjuvant), but the concomitant component is crucial to potentiate RT. Long-term ADT, ranging from two to three years is recommended for locally advanced disease [416, 456] rather than short term (six months) [455]. Dose escalation phase III RCTs are on-going to assess its impact on DFS. Cardiovascular mortality may be related to ADT, not RT, as addressed in Section 8.2

Whether these results should be applied to patients with intermediate- or high-risk localised PCa is unclear. The Boston trial has shown an improved eight-year OS rate for patients without moderate or severe comorbidity assigned to six months of complete ADT ($p = 0.01$) [454], and the RTOG 94-08 study showed an increased ten-year OS rate for intermediate risk only with four months of complete ADT ($p = 0.003$) [415].

The EORTC trial 22961, an equivalence trial with 970 patients (78% T3-4, 92% N0) combined RT (70 Gy) with either six months or with three years of LHRH analogue treatment. With a median follow-up of 6.4 years, both CSS and overall mortality were significantly lower with long-term androgen suppression [416].

In the RTOG 9910 trial, 1,579 intermediate-risk PCa patients were randomised to LHRH antagonist therapy for eight weeks before RT (70.2 Gy in 2-D or 3-D techniques) followed by either another eight or 28 weeks of anti-hormonal treatment. Extended androgen suppression did not significantly improve ten-year rates of distant (both arms 6%), loco-regional (6% vs. 4%) or biochemical progression (both arms 27%), or DSS (96% vs. 95%) or OS (66% vs. 67%). The 8 + 8 week scheme was confirmed as a standard procedure [457].

Table 6.3.3: Studies of use and duration of androgen deprivation therapy in combination with radiotherapy for prostate cancer

Trial	TNM stage	n	Trial	ADT	RT	Effect on OS
EORTC 22863, 2010 [451]	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRH agonist for 3 yr. (adjuvant)	70 Gy RT	Significant benefit at ten yr. for combined treatment (HR: 0.60, 95% CI: 0.45-0.80, $p = 0.0004$).
RTOG 85-31, 2005 [452]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65-70 Gy RT	Significant benefit for combined treatment ($p = 0.002$) seems to be mostly caused by patients with GS 7-10
Granfors, <i>et al.</i> 2006 [458]	T3 N0-1 M0	91	EBRT ± ADT	Orchiectomy	65 Gy RT	Significant benefit ($p = 0.02$ $p = 0.03$), mainly caused by LN-positive tumours
D'Amico, <i>et al.</i> 2008 [454]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	Significant benefit (HR: 0.55, 95% CI: 0.34-0.90, $p = 0.01$) that may pertain only to men with no, or minimal, comorbidity TROG 96-01

Denham, <i>et al.</i> 2011 [455]	T2b-4 N0 M0	802	Neoadjuvant ADT duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	No significant difference in OS reported; benefit in PCa-specific survival (HR: 0.56; 95% CI: 0.32-0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65-1.08; p = 0.18)
RTOG 94-13, 2007 [459]	T1c-4 N0-1 M0	1292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)
RTOG 86-10, 2008 [453]	T2-4 N0-1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65-70 Gy RT	No significant difference at 10 yr.
RTOG 92-02, 2008 [456]	T2c-4 N0-1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 years as adjuvant after 4 mo. as neoadjuvant	65-70 Gy RT	p = 0.73 p = 0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with GS 8-10
EORTC 22961, 2009 [416]	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr.	70 Gy 3D-CRT	Better result with 3-year treatment than with 6 mo. (3.8% improvement in survival at 5 yr.)
Pisansky, <i>et al.</i> 2014 [457]	intermediate risk (94% T1-T2, 6% T3-4)	1579	Short vs. prolonged ADT	LHRH antagonist 8 + 8 vs. 8 + 28 wk	70.2 Gy 2D/3D	67 vs. 68% p = 0.62, confirms 8 + 8 weeks LHRH as a standard
SPCG-7/SFUO-3, 2014 [460]	T1b-2 Grade 2-3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo plus continuous flutamide	70 Gy 3D-CRT vs. no RT	18.9% (30.7%) vs. 8.3% (12.4%) cancer specific mortality at 10 (15) yr. favouring combined treatment (HR: 0.35; p < 0.0001 for 15 yr. results) NCIC CTG PR.3/MRC
PRO7/SWOG, 2014, 2015 [461, 462]	T3-4 (88%), PSA > 20 ng/mL (64%), GLS 8-10 (36%) N0 M0	1205	ADT ± EBRT	Continuous LHRH agonist	65-70 Gy 3D-CRT vs. no RT	10 yr. OS = 49% vs. 55% favouring combined treatment (HR: 0.7, p < 0.001)
Mottet, <i>et al.</i> 2012 [463]	T3-4 N0 M0	273 264	ADT ± EBRT	LHRH agonist for 3 yr.	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5 yr. OS 71.4% vs. 71.5%

ADT = androgen deprivation therapy; EBRT = external beam radiation therapy; GS = Gleason score; LHRH = luteinising-hormone-releasing hormone; OS = overall survival; RT = radiotherapy; HR = hazard ratio; 3D-CRT = three-dimensional conformal radiotherapy.

6.3.3.4 *Neoadjuvant chemotherapy plus radiotherapy*

The GETUG 12 trial investigated the impact of neoadjuvant chemotherapy with docetaxel on the PFS in a cohort of 413 high-risk patients. Patients were randomly assigned to either goserelin 10.8 mg every three months for three years, plus four cycles of docetaxel and estramustine or to goserelin alone (arm 2). Local therapy was administered at three months and consisted of RT in 358 patients (87%). Toxicity included Grade 3-4 neutropenia (27%) with neutropenic fever in 2%, but no toxicity-related death. A PSA response (PSA < 0.2 ng/mL after three months of treatment) was obtained in 34% in the ADT + docetaxel arm and 15% in the ADT arm. With a median follow-up period of 4.6 years, the four-year PFS was 85% in arm 1 vs. 81% in arm 2 ($p = 0.26$), but the data need to mature [464].

6.3.3.5 *Combined dose-escalated radiotherapy and androgen-deprivation therapy*

Zelevsky *et al.* [465] reported a retrospective analysis comprising 571 patients with low-risk PCa (22.4%), 1,074 with intermediate-risk PCa (42.1%), and 906 with high-risk PCa (35.5%). Three-dimensional-conformal RT or IMRT were administered. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last ten years of the study using image-guided IMRT. Complete androgen blockade was administered at the discretion of the treating physician to 623 high-risk PCa (69%), 456 intermediate-risk PCa (42%) and 170 low-risk PCa (30%) patients. The duration of ADT was three months for low-risk patients and six months for intermediate-risk and high-risk patients, starting three months before RT. The ten-year biochemical disease-free rate (BDFR) was significantly improved by dose escalation: 84% (> 75.6 Gy) vs. 70% for low-risk PCa ($p = 0.04$), 76% (> 81 Gy) vs. 57% for intermediate-risk PCa ($p = 0.0001$), and 55% (> 81 Gy) vs. 41% for high-risk patients ($p = 0.0001$). The six-month ADT also influenced the BDFR in intermediate- and high-risk patients, with 55% for intermediate-risk vs. 36% for high-risk patients ($p < 0.0001$). In the multivariate analysis, a dose > 81 Gy ($p = 0.027$) and ADT ($p = 0.052$) were found to be predictive factors for distant metastasis-free survival, but none of these parameters influenced OS.

6.3.3.6 *Recommended external beam radiation therapy treatment policy for localised PCa*

6.3.3.6.1 Low-risk PCa

Intensity-modulated RT with escalated dose without ADT is an alternative to brachytherapy (see below).

6.3.3.6.2 Intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT with short-term ADT (four to six months) [415, 466, 467]. For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT at an escalated dose (76-80 Gy) or a combination of IMRT and brachytherapy.

6.3.3.6.3 Localised high-risk PCa

The high risk of relapse outside the irradiated volume makes it mandatory to use a combined modality approach, consisting of dose-escalated IMRT, possibly including the pelvic lymphatics + long-term ADT. The duration of ADT has to take into account WHO PS, comorbidities, and the number of poor prognostic factors. It is important to recognise that EBRT + short-term ADT did not improve OS in high-risk localised PCa, in the Boston and RTOG 94-13 and 86-10 trials [453, 454, 459], and long-term ADT is currently recommended for these patients.

6.3.3.6.4 Locally advanced PCa: T3-4 N0, M0

In locally advanced disease, RCTs have clearly established that the additional use of long-term ADT combined with RT produces better OS. Whilst RT is effective in this patient group, combined RT + ADT is clearly superior to ADT alone.

6.3.3.6.5 MRC PR3/PR07 study - The National Cancer Institute of Canada (NCIC)/UK Medical Research Council (MRC)/Southwest Oncology Group (SWOG) intergroup PR3/PR07 study

This study comprised 1,205 patients, consisting of T3-4 ($n = 1,057$), or T2, PSA > 40 ng/mL ($n = 119$), or T2, PSA > 20 ng/mL and Gleason score > 8 ($n = 25$), who were randomly assigned to lifelong ADT (bilateral orchidectomy or LHRH agonist), with or without RT (65-70 Gy to the prostate, with or without 45 Gy to the pelvic LNs). With a median follow-up of eight years, OS was significantly improved in the patients allocated to ADT + RT (HR: 0.70; 95% CI: 0.57-0.85; $p < 0.001$). Deaths from PCa were significantly reduced by the addition of RT to ADT (HR: 0.46; 95% CI: 0.34-0.61; $p < 0.001$). Patients on ADT + RT reported a higher frequency of adverse events related to bowel toxicity, but only two of 589 patients had Grade 3 or greater diarrhoea at 24 months after RT [462].

A total of 273 patients with locally advanced PCa T3-4 or pT3 N0 M0 were randomly assigned to three years

of ADT using an LHRH agonist (leuprorelin), with or without RT (70 Gy to the prostate plus 48 ± 2 Gy to the pelvic LNs). After a median follow-up period of 67 months, there was a significant improvement in the five-year DFS ($p < 0.001$), metastatic DSS ($p < 0.018$), and loco-regional PFS ($p < 0.0002$), but the effect on OS was not reported [463].

Another study compared hormonal treatment alone (i.e. three months of continuous androgen blockade followed by continuous flutamide treatment ($n = 439$) with the same treatment combined with RT ($n = 436$) [460]. The ten (fifteen) year cumulative PCSM was 18.9% (30.7%) and 8.3% (12.4%) (HR: 0.35; [$p < 4.1E-10$ for fifteen year results]), and overall mortality was 35.3% (56.7%) and 26.4% (43.4%) (HR: 0.70; $p = 0.0006$ for fifteen-year results), respectively.

6.3.3.7 *Lymph node irradiation*

6.3.3.7.1 Prophylactic LN irradiation in clinically N0 prostate cancer (estimated cN0)

There is no level 1 evidence for prophylactic whole-pelvic irradiation, since RCTs have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic LNs in high-risk cases. Such studies include the RTOG 77-06 study ($n = 484$ with T1b-T2) [468], the Stanford study ($n = 91$) [469], and the GETUG 01 trial ($n = 444$ with T1b-T3 N0 pNx M0) [470]. In the RTOG 94-13 study [459], there were no differences in the PFS in patients treated with whole-pelvic or prostate-only RT, but interactions between whole-pelvic RT and the duration of ADT were reported following the subgroup analysis. Pelvic LND may be needed to improve the selection of patients who may be able to benefit from pelvic LN irradiation and to supplement the use of the Briganti tables [340] and/or the Roach formula [471]. The results of pelvic LND, especially in young patients, allows radiation oncologists to tailor both the planning target volume and the duration of ADT, particularly ensuring that there is no pelvic irradiation for pN0 patients, while it is possible to irradiate, in combination with long-term ADT. The real impact of such an approach remains, so far, hypothetical, since no randomised trials are available. The benefits of pelvic nodal irradiation at a high dosage using IMRT merit further investigation in a phase II trial. One such trial is currently recruiting through the RTOG, and PIVOTAL, a UK randomised phase II trial, has completed accrual.

6.3.3.7.2 Clinical, or pathological node positive, M0 disease

Outcomes in this group after RT as a sole modality are poor [416], and these patients should receive RT plus long-term ADT. The RTOG 85-31 randomised phase III trial, with a median follow-up period of 6.5 years, showed that 95 of the 173 pN1 patients who received pelvic RT with immediate HT had better five-year (54%) and nine-year (10%) PFS rates (PSA < 1.5 ng/mL) vs. 33% and 4%, respectively, for radiation alone ($p < 0.0001$). Multivariate analysis showed that this combination had a statistically significant impact on the OS [472]. Patients with pelvic LN involvement lower than the iliac regional nodes, < 80 years old, with a WHO PS 0-1 and no severe comorbidity, may be candidates for EBRT + immediate long-term HT. Recent data from the UK Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) trial suggests that pelvic RT could be beneficial for N1 disease, but this is not based on a randomised comparison [473] (see also Section 6.3.7).

6.3.4 **Proton beam therapy**

In theory, proton beams are an attractive alternative to photon-beam RT for PCa, as they deposit almost all their radiation dose at the end of the particle's path in tissue (the Bragg peak), in contrast to photons, which deposit radiation along their path. There is also a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.

Two recent planning studies comparing conformal proton therapy with IMRT have yielded conflicting results; one study suggested that the two are equivalent in terms of rectal dose sparing, but that IMRT is actually superior in terms of bladder sparing [474]; the other study suggested a clearer advantage for protons [475].

One RCT on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose, but it cannot be used as evidence for the superiority of proton therapy per se [411]. Thus, unequivocal information that shows an advantage of protons over IMRT photon therapy is still not available.

Studies from the SEER database, and from Harvard [476, 477], describing toxicity and patient reported outcomes do not point to an inherent superiority for protons. In terms of longer term gastrointestinal (GI) toxicity, proton therapy might even be inferior to IMRT [477].

A retrospective 2:1 matched-control analysis of 27,647 U.S. Medicare patients compared 314 men receiving proton therapy with 628 men who had IMRT. Despite the considerably higher costs for proton

therapy, there was some improvement in GU-tract toxicity after 6 months, but not after 12 months, and not at the GI tract [478].

A randomised trial comparing equivalent doses of proton-beam therapy with IMRT is needed to compare the efficacy of protons vs. photons; a study of this type is under consideration by the RTOG. Meanwhile, proton therapy must be regarded as a promising, but experimental, alternative to photon-beam therapy.

6.3.5 **Low-dose rate and high-dose rate brachytherapy**

6.3.5.1 *Low-dose rate (LDR) brachytherapy*

There is a consensus on the following eligibility criteria for LDR monotherapy [479]:

- stage cT1b-T2a N0, M0;
- Gleason score 6 with \leq 50% of biopsy cores involved with cancer or;
- Gleason score 3 + 4 with \leq 33% of biopsy cores involved with cancer;
- an initial PSA level of \leq 10 ng/mL;
- a prostate volume of $<$ 50 cm³;
- an International Prostatic Symptom Score (IPSS) \leq 12 and maximal flow rate $>$ 15 mL/min on urinary flow tests [408].

Low-dose rate brachytherapy uses radioactive seeds permanently implanted into the prostate. Patients with low- and favourable intermediate-risk PCa are the most suitable candidates for LDR brachytherapy as monotherapy. The use of guidelines is strongly recommended [479-481]. There have been no RCTs comparing brachytherapy as monotherapy with other curative treatment modalities. Outcome data are available from a number of large population cohorts with mature follow-up [482-489]. The BDFS for Gleason 6 patients after five and ten years has been reported to range from 71% to 93% and 65% to 85%, respectively [482-489].

A significant correlation has been shown between the implanted dose and recurrence rates [490]. Patients receiving a D90 (dose covering 90% of the prostate volume) of $>$ 140 Gy had a significantly higher biochemical control rate (PSA $<$ 1.0 ng/mL) after four years than patients who received less than 140 Gy (92 vs. 68%).

In men with intermediate- or high-risk PCa, LDR brachytherapy boost with supplemental EBRT and hormonal treatment [491] may be considered. Dose-escalated EBRT has been compared with EBRT and LDR brachytherapy boost in intermediate-risk and high-risk patients in a RCT [492]. The ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) multi-centre Canadian trial compared EBRT (total dose of 78 Gy) to EBRT (total dose 46 Gy) followed by LDR brachytherapy boost (prescribed dose 115 Gy). The use of LDR boost resulted in five- and seven-year PSA PFS rates of 89% and 86%, respectively compared to 84% and 75% in those treated with EBRT alone. This improvement in PSA control came with an increase in late urinary toxicity with 18% experiencing G3+ toxicity in the LDR boost arm as compared to 8% in the EBRT alone arm. Toxicity was mainly due to urethral strictures and incontinence and great care should be taken during treatment planning.

6.3.5.2 *High-Dose Rate (HDR) brachytherapy*

High-dose rate brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. The technical differences are outlined in the table below. The use of published guidelines is strongly recommended [493]. High-dose rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [494]. A single RCT of EBRT vs. EBRT and HDR brachytherapy boost has been reported [495]. A total of 218 patients with organ-confined PCa were randomised to EBRT alone with a dose of 55 Gy in twenty fractions, or EBRT with a dose of 35.75 Gy in thirteen fractions, followed by HDR brachytherapy with a dose of 17 Gy in two fractions over 24 hours. In comparison with EBRT alone, the combination of EBRT and HDR brachytherapy showed a significant improvement in the BDFR ($p = 0.04$) with five-, seven- and ten-year estimates of biochemical control of 75%, 66% and 46% for combination treatment compared to 61%, 48% and 39% for external beam alone. There were no differences in the rates of late bowel, urinary or sexual patient QoL over a ten-year follow-up period. However, a very high, uncommon rate of early recurrences was observed in the EBRT arm alone, even after two years, possibly due to a dose lower than the current standard used [495]. A SR of non-randomised trials has suggested the possibility that outcomes with EBRT plus HDR brachytherapy are superior to brachytherapy alone, but this needs confirmation in a prospective RCT [496].

Fractionated HDR brachytherapy as monotherapy can be offered to patients with low and intermediate-risk PCa, who should be informed that results are only available from limited series in very experienced centres [497, 498]. Five year PSA control rates over 90% are reported, with late G3+ genito-urinary toxicity rates $<$ 5% and no, or very minimal, G3+ gastro-intestinal toxicity rates [497, 498].

	Differences in prostate brachytherapy techniques
Low Dose Rate (LDR)	<ul style="list-style-type: none"> • Permanent seeds implanted • Uses I-125 (most common), Pd-103 or Cs-131 isotopes • Radiation dose delivered over weeks and months • Acute side effects resolve over months • Radiation protection issues for patient and carers
High Dose Rate (HDR)	<ul style="list-style-type: none"> • Temporary implantation • Ir-192 isotope introduced through implanted needles or catheters • Radiation dose delivered in minutes • Acute side effects resolve over weeks • No radiation protection issues for patient or carers

A SR and meta-analysis of observational studies comparing patients exposed or unexposed to RT in the course of treatment for PCa demonstrate an increased risk of developing second cancers for bladder (OR 1.39), colorectal (OR 1.68) and rectum (OR 1.62) with similar risks over lag times of five and ten years. Absolute risks over ten years are small (1-4%) but should be discussed with younger men in particular [499].

6.3.6 **Immediate (adjuvant) post-operative external irradiation after RP (cN0 or pN0) (Table 6.3.5)**

Extracapsular invasion (pT3), Gleason score ≥ 7 and positive surgical margins (R1) are associated with a risk of local recurrence, which can be as high as 50% after five years [500]. Three prospective RCTs have assessed the role of immediate post-operative RT (adjuvant RT [ART]), as follows:

6.3.6.1 *EORTC 22911*

EORTC 22911 [501], with a target sample size of 1,005 patients, compared immediate post-operative RT (60 Gy) with RT delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 with risk factors R1 and pT2R1 after radical retropubic prostatectomy (RRP). Grade 4 toxicity was not observed (for criteria: see Tables 8.2.2 and 8.2.3). The rate of Grade 3 GU toxicity was 5.3% vs. 2.5% in the observation group after ten years. For patients younger than 70 years, the study concluded that immediate post-operative RT after surgery significantly improved the ten-year biological PFS to 60.6% vs. 41.1% in the observation group. Local-regional control was better in the long-term follow-up at ten years after immediate irradiation (HR: 0.45; $p < 0.0001$). However, ART patients with pT2-3 R1 also showed an improved clinical PFS after ten years (HR: 0.69; $p = 0.008$). Overall survival did not differ significantly between the treatment arms. After re-evaluation using a central pathological review, the highest impact of ART was on biochemical progression (HR reduced to 0.3) seen in patients with positive margins, but there was also a positive effect of 10% after five years for pT3 with negative margins and other risk factors [501].

6.3.6.2 *ARO trial*

The conclusions of ARO trial 96-02 ($n = 385$) appear to support those of the EORTC study. After a median follow-up period of 112 months, the RT group (60 Gy) demonstrated a significant improvement in BDFR of 56% vs. 35%, respectively ($p = 0.0001$). However, unlike other studies, and of major interest, the randomisation of patients was carried out after they had achieved an undetectable PSA level following RP (< 0.1 ng/mL) and only pT3 tumours were included. This result indicates that ART is effective, even in the setting of an undetectable PSA after RP and additional risk factors [502].

6.3.6.3 *SWOG 8794 trial*

Conversely, the updated results, with a median follow-up of more than twelve years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a ten-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, $p = 0.016$) and a ten-year OS of 74% vs. 66% (median: 1.9 years prolongation; $p = 0.023$) [503, 504].

6.3.6.4 *Conclusion*

Thus, for patients classified as pT3 pN0 with a high risk of local failure after RP due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of < 0.1 ng/mL, two options can be offered in the framework of informed consent. These are:

- immediate ART to the surgical bed [501, 502, 504] after recovery of urinary function.
- or
- clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [505, 506] (see Section 6.10.5.1).

Table 6.3.4: Overview of all three randomised trials for adjuvant radiation therapy after radical prostatectomy*

Reference	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical PFS survival	OS
SWOG 8794, 2009 [504]	431	pT3 cN0 ± involved SM	60-64 Gy vs. observation	> 0.4	152	10 yr: 53% vs. 30% (p < 0.05)	10 yr.: 74% vs. 66% Median time: 15.2 vs. 13.3 yr. p = 0.023
EORTC 22911, 2012 [501]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs. observation	> 0.2	127	10 yr: 60.6% vs. 41% (p < 0.001)	81% vs. 77% n.s.
ARO 96-02, 2014 [502]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs. observation	> 0.05 + confirmation	112	10 yr: 56% vs. 35% (p = 0.0001)	10 yr.: 82% vs. 86% n.s.

*See Section 6.10.5.1 for delayed (salvage) post-radical prostatectomy external irradiation.

BCR = biochemical recurrence; n = number of patients; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

6.3.7 Summary of evidence and guidelines for definitive radiotherapy

Summary of evidence	LE
The highest effect of adjuvant radiotherapy is seen in patients with pT3R1 PCa.	1a
The optimum duration of androgen deprivation therapy (ADT) with external beam radiation therapy (EBRT) is well established in the literature. There is no evidence that these durations should change when using brachytherapy boost with EBRT.	1b
Limited data, from experienced centres only, are available for the use of fractionated high-dose-rate brachytherapy as monotherapy in patients with low and intermediate-risk PCa.	2a

Recommendations	LE	GR
Offer external beam radiation therapy (EBRT) to all risk groups of non-metastatic PCa	1b	A
In low-risk PCa, use a total dose of 74 to 78 Gy.	1a	A
In patients with low-risk PCa, and selected intermediate-risk PCa, without a previous transurethral resection of the prostate (TURP) and with a good International Prostate Symptom Score and a prostate volume < 50 mL, offer low-dose rate (LDR) brachytherapy.	2a	A
In patients with intermediate-risk PCa use a total dose of 76-78 Gy, in combination with short-term ADT (four to six months).	1b	A
In patients with high-risk localised PCa and locally advanced cN0 PCa, use EBRT to a dose of 76-78 Gy, or combined EBRT with brachytherapy boost (either high-dose rate [HDR] or LDR). Radiotherapy should be given in combination with long-term androgen deprivation therapy (two to three years).	1a EBRT	A
	1b brachytherapy	
Offer intensity-modulated radiotherapy (IMRT) for definitive treatment of PCa by EBRT.	2a	A
Moderate hypofractionation (HFX) with IMRT including image-guided radiation therapy (IGRT) to the prostate only can be offered to carefully selected patients with localised disease (as discussed in the text).	1a	A
Moderate HFX should adhere to radiotherapy-protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.	1a	A

In patients with cN+ or pN+ PCa offer pelvic external irradiation in combination with immediate long-term ADT.	2b	B
In patients with pT3, N0M0 PCa and an undetectable prostate-specific antigen (PSA) following radical prostatectomy, discuss adjuvant EBRT because it improves at least biochemical-free survival.	1a	A
Inform patients with an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases (see Section 6.9.5.1).	1b	A

6.4 Treatment: Options other than surgery and radiotherapy for the primary treatment of localised prostate cancer

6.4.1 Background

Besides RP, EBRT and brachytherapy, other modalities have emerged as therapeutic options in patients with clinically localised PCa [507-510]. In this section, both whole gland and focal treatment will be considered, looking particularly at high-intensity focused US (HIFU) and cryosurgical ablation of the prostate (CSAP) as sufficient data are available to form the basis of some initial judgements on these latest additions to the management of PCa. Other options - such as photodynamic therapy, radiofrequency ablation and electroporation, among others - are considered to be in the early phases of evaluation and will therefore not be discussed in this edition of the Guidelines. Both HIFU and CSAP have been developed as minimally invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity and improved functional outcomes. In addition, a relatively newer development is focal ablative therapy, whereby lesion-targeted ablation is undertaken in a precise, organ-sparing manner.

6.4.2 Cryosurgery

Cryosurgery uses freezing techniques to induce cell death by:

- dehydration resulting in protein denaturation;
- direct rupture of cellular membranes by ice crystals;
- vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [507-510].

Freezing of the prostate is ensured by the placement of 12-15 x 17 gauge cryoneedles under TRUS guidance, placement of thermosensors at the level of the external sphincter and bladder neck, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance, resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle. Currently, third and fourth generation cryosurgery devices are mainly used.

Potential candidates for CSAP are those who have organ-confined PCa and those identified as having minimal tumour extension beyond the prostate [507-509], The PSA should be < 20 ng/mL, and the Gleason score should be < 7:

- patients with low-risk PCa, or intermediate-risk PCa whose condition prohibits RT or surgery;
- at the time of therapy, the size of the prostate should be < 40 mL; volume reduction may be achieved by androgen ablation to avoid any technical difficulty in placing cryoprobes under the pubic arch.

It is important that patients with a life expectancy > 10 years should be fully informed that there are limited data on the long-term outcome for cancer control > 10 years and that this treatment modality is still considered as experimental.

6.4.2.1 Results of cryosurgery for PCa

A comparative assessment of primary ablative therapies for localised PCa, including CSAP, was recently undertaken by Ramsay *et al.* [511]. The SR and network meta-analysis compared CSAP vs. RP and EBRT. Data from 3,995 patients across nineteen studies (including one RCT, four non-randomised comparative studies, and fourteen case series) were included. In the short-term, there was conflicting evidence relating to cancer-specific outcomes when CSAP was compared with either EBRT or RP. The only finding that reached statistical significance was one-year DFS, which was worse for cryotherapy than for either EBRT or RP. However, none of the other cancer-specific outcomes, such as BCF or OS, showed any significant differences. Overall, because of the high risk of bias across the studies, the findings for cancer-specific outcomes were considered inconclusive. The review noted significant inconsistencies in outcome definitions, measurement and reporting in the evidence base, in particular BCR.

6.4.3 High-intensity focused ultrasound of the prostate

High-intensity focused ultrasound consists of focused US waves, emitted from a transducer, that cause tissue

damage by mechanical and thermal effects as well as by cavitation [512]. The goal of HIFU is to heat malignant tissues above 65°C so that it is destroyed by coagulative necrosis. High-intensity focused ultrasound is performed under general or spinal anaesthesia, with the patient lying in the lateral position. Potential candidates are patients with low-to-moderate risk as part of clinical trials. The patient should be informed about the lack of long-term outcome data at > 10 years (see Section 7.4.4.2).

6.4.3.1 Results of high-intensity focused ultrasound in PCa

As with CSAP, various PSA thresholds are defined for biochemical cure, and no international consensus exists on objective response criteria. The Stuttgart criteria (> PSA nadir + 1.2 ng/mL) have been proposed to define BCR after HIFU treatment [513].

A recent SR and comparative assessment by network meta-analysis [511] compared HIFU vs. RP and EBRT as primary treatment for localised PCa. Data from 4,000 patients across 21 studies (including one non-randomised comparative study and 20 case series) were included. There was some evidence that BCF rates were significantly higher at one year with HIFU than with EBRT. However, the difference was no longer statistically significant at five years. Similar statistically significant findings were observed with regard to DFS at one year, with worse outcomes for HIFU than for EBRT. The differences were no longer significant at three years. At four years, in contrast to OS, the biochemical result was higher when using HIFU.

In an earlier SR and meta-analysis [514], 150 papers related to HIFU were identified and evaluated with regard to various oncological and functional outcome parameters [514]. No RCT was available for analysis, and no survival data were presented. No validated biochemical surrogate end-point was available for HIFU therapy. The review found HIFU to be associated with a PFS (based on PSA ± biopsy data) of 63-87% (projected three- to five-year data), but median follow up in the studies ranged from 12-24 months only.

6.4.4 Focal therapy of PCa

During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this has been to identify men at an earlier stage with smaller tumours that occupy only 5-10% of the prostate volume, with a greater propensity for unifocal or unilateral disease [515-517]. Most focal therapies to date have been achieved with ablative technologies: cryotherapy, HIFU, photodynamic therapy, electroporation, and focal RT by brachytherapy or CyberKnife Robotic Radiosurgery System technology (Accuray Inc., Sunnyvale, CA, USA). The main purpose of focal therapy is to ablate tumours selectively whilst limiting toxicity by sparing the neurovascular bundles, sphincter and urethra [518-520].

Ramsay *et al.*'s [502] SR and network meta-analysis of ablative therapy in men with localised PCa performed a sub-group analysis of focal therapy vs. RP and EBRT. Nine case series reporting on focal therapy were identified (five studies reporting on focal CSAP, three studies on focal HIFU, and one study reporting on both). For focal CSAP vs. RP or EBRT, no statistically significant differences were found for BCR at three years. For focal HIFU vs. RP or EBRT, there were no comparable data on oncological, continence nor potency outcomes at one year or more. More recently, Valerio *et al.* [521] performed a SR to summarise the evidence regarding the effectiveness of focal therapy in localised PCa. Data from 3,230 patients across 37 studies were included, covering different energy sources including HIFU, CSAP, photodynamic therapy, laser interstitial thermotherapy, focal brachytherapy, irreversible electroporation and radiofrequency ablation. The overall quality of the evidence was low, due to the majority of studies being single-centre, non-comparative and retrospective in design, heterogeneity of definitions, approaches, follow-up strategies, outcomes, and duration of follow-up. Although the review suggests that focal therapy has a favourable toxicity profile in the short to medium-term, its oncological effectiveness remains unproven due to lack of reliable comparative data against standard interventions such as RP and EBRT. Robust prospective trials reporting standardised outcomes [522] are needed before recommendations in support of focal therapy for routine clinical practice can be made.

6.4.5 **Summary of evidence and guidelines for experimental therapeutic options to treat clinically localised prostate cancer**

Summary of evidence	LE
The available short-term data regarding cryosurgery and high-intensity focused ultrasound (HIFU) does not prove equivalence to standard interventions.	2b
There is no reliable long-term comparative data to indicate that cryosurgery or HIFU leads to equivalent oncological outcomes compared with radical prostatectomy or external beam radiation therapy.	3
Prostate specific antigen nadir values after ablative therapies may have prognostic value.	3
Focal therapy of any sort appears promising but remains investigational, with uncertainties surrounding outcome definitions, follow-up and re-treatment criteria.	3

Recommendations	LE	GR
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting.	3	A
Only offer focal therapy within a clinical trial setting.	3	A

6.5 **Treatment: Hormonal therapy - rationale and available drugs**

6.5.1 **Introduction**

6.5.1.1 *Different types of hormonal therapy*

Androgen deprivation can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor. These two methods can be combined to achieve what is known as complete (or maximal or total) androgen blockade (CAB) [523].

6.5.2 **Testosterone-lowering therapy (castration)**

6.5.2.1 *Castration level*

Surgical castration is still considered the primary treatment modality for ADT. It leads to a considerable decline in testosterone levels: the 'castration level'.

The castrate level is < 50 ng/dL (1.7 nmol/L), which was defined more than 40 years ago, when testosterone testing was limited. Current methods have shown that the mean value after surgical castration is 15 ng/dL [524]. Therefore, a more appropriate level is defined as < 20 ng/dL (1 nmol/L). This new definition is important as better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL [525-527]. However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is still < 50 ng/dL (1.7 mmol/L).

6.5.2.2 *Bilateral orchiectomy*

Bilateral orchiectomy, or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia [528] and it is the quickest way to achieve a castration level, which is usually reached within less than twelve hours. It is irreversible and does not allow for intermittent treatment.

6.5.3 **Oestrogens**

Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [529]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side effects, especially thromboembolic complications, even at lower doses [530, 531] these drugs are not considered as standard first-line treatment.

6.5.4 **Luteinising-hormone-releasing hormone agonists**

Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH, are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they induce a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosterone surge' or 'flare-up' phenomenon, which starts two to three days after administration and lasts for about one week. The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection.

6.5.4.1 *Achievement of castration levels*

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and

FSH secretion and therefore testosterone production. A castration level is usually obtained within two to four weeks [532]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [533] and comparable to orchiectomy [533, 534].

6.5.4.2 'Flare-up' phenomenon

The 'flare-up' phenomenon might lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status [535].

Patients at risk are usually those with high-volume, symptomatic, bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely remove the risk.

6.5.5 Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with only monthly formulations being available.

Degarelix

Degarelix is an LHRH antagonist. The standard dosage is 240 mg in the first month, followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [536]. An extended follow-up has been published, suggesting a better PFS compared to monthly leuporelin [536]. Its definitive superiority over the LHRH analogues remains to be proven.

6.5.6 Anti-androgens

These oral compounds are classified according to their chemical structure as:

- steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal anti-androgens and leads to an unchanged or slightly elevated testosterone level. Conversely, steroidal anti-androgens have progestational properties leading to central inhibition by crossing the blood-brain barrier.

6.5.6.1 Steroidal anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side-effects are secondary to castration (gynaecomastia is quite rare) whilst the non-pharmacological side effects are cardiovascular toxicity (4-40% for cyproterone acetate [CPA]) and hepatotoxicity.

6.5.6.1.1 Cyproterone acetate

Cyproterone acetate was the first licensed anti-androgen, but the least studied. Its most effective dose as monotherapy is still unknown. Although CPA has a relatively long half-life (31-41 hours), it is usually administered in two or three fractionated doses of 100 mg each. In one RCT [537] CPA showed a poorer OS when compared with LHRH analogues. An underpowered RCT comparing CPA monotherapy with flutamide in M1b PCa did not show any difference in disease-specific and OS at a median follow-up of 8.6 years [538]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.5.6.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [539]. Non-androgen pharmacological side effects differ between agents, with bicalutamide showing a more favourable safety and tolerability profile than flutamide and nilutamide [540]. All three agents share a common potential liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

6.5.6.2.1 Nilutamide

Nilutamide monotherapy has not been compared to castration and is not licensed for monotherapy. Non-androgen pharmacological side effects are visual disturbances (i.e. delayed adaptation to darkness), alcohol intolerance, nausea, and specifically severe interstitial pneumonitis (potentially life-threatening).

6.5.6.2.2 Flutamide

Flutamide has been studied as monotherapy. Flutamide is a pro-drug, and the half-life of the active metabolite is five-six hours, allowing for a three times daily dose. The recommended total daily dosage is 750 mg. The

non-androgen pharmacological side-effect of flutamide is diarrhoea.

6.5.6.2.3 Bicalutamide

The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%). However, bicalutamide monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [539, 541].

6.5.7 **New compounds (for castrate-resistant patients only)**

During castration, the occurrence of castration-resistance (CRPC) is systemic. It is considered to be mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent (see Section 6.10 - Castrate-resistant PCa). In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells, and an over-expression of the AR has been observed, suggesting an adaptive mechanism [542]. This has led to the development of two new compounds targeting the androgen axis: abiraterone acetate and enzalutamide. Both are currently approved for mCRPC only.

6.5.7.1 *Abiraterone acetate*

Abiraterone acetate (AA) is a CYP17 inhibitor (a combination of 17 α -hydroxylase and 17,20-lyase inhibition). By blocking CYP17, AA significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside the cancer cells (intracrine mechanism). This compound must be used together with prednisone/prednisolone (2 x 5 mg) to prevent drug-induced hyperaldosteronism.

6.5.7.2 *Enzalutamide*

Enzalutamide is a novel anti-androgen with a higher affinity than bicalutamide for the AR receptor. While non-steroidal anti-androgens still allow transfer of ARs to the nucleus, enzalutamide also blocks AR transfer and therefore suppresses any possible agonist-like activity.

6.5.8 **Cost-effectiveness of hormonal therapy options**

A formal meta-analysis evaluated the cost-effectiveness of various long-term androgen suppression options in advanced PCa. For men who can accept it, bilateral orchiectomy is the most cost-effective form of ADT, providing a higher quality-adjusted survival, while CAB is the least economically attractive option, yielding small health benefits at relatively high costs. Furthermore, the greatest QoL gains and least costs may be obtained by starting ADT when symptoms from distant metastases have occurred [543]. Finally, once ADT is started and if a major response is obtained, intermittent androgen deprivation (IAD) may be an effective option to lower treatment costs.

6.6 **Treatment: Metastatic prostate cancer**

6.6.1 **Introduction**

A SR of ADT in PCa has recently been published [523].

6.6.2 **Prognostic factors**

Median survival of patients with newly diagnosed metastases is at least 42 months [544] but the M1 population is very heterogeneous. Several prognostic factors for survival have been suggested including the number and location of bone metastases, visceral metastases, Gleason score, PS status and initial PSA [545], alkaline phosphatase [546], but none of these have been validated in a direct comparison. In clinical trials, the number and location of bone metastases and the presence of visceral lesion are the prognostic factors most often used [547].

Based on a large SWOG 9346 cohort, the PSA level after seven months of ADT was used to create three prognostic groups, group 1 with a PSA < 0.2 ng/mL and a median survival of 75 months, group 2 with a PSA < 4 ng/mL with a median survival of 44 months and group 3 with a PSA > 4 ng/mL and only thirteen months median survival [548]. This grouping, however, requires independent confirmation.

6.6.3 **First-line hormonal treatment**

Primary ADT has been the standard of care for over 50 years [523]. There is no level 1 evidence for, or against, a specific type of ADT, whether orchiectomy, an LHRH analogue or antagonist, except in patients with impending spinal cord compression for whom either a bilateral orchidectomy, or an LHRH antagonist are the preferred options.

6.6.3.1 Prevention of 'flare-up'

The initial testosterone flare associated with LHRH agonists can be prevented by co-administration of an anti-androgen [549]. Prevention of 'flare-up' is important in symptomatic patients or when a clinical flare might lead to severe complications. Anti-androgen therapy is usually continued for four weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. In addition, the long-term impact of preventing 'flare-up' is unknown [550].

6.6.4 Combination therapies

6.6.4.1 Complete androgen blockade

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [551]. However, results with other anti-androgens or castration modalities have differed and SRs have shown that CAB using a non-steroidal anti-androgen (NSAA) appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [552, 553] beyond five years of survival [554] but this minimal advantage in a small subset of patients must be balanced against the increased side effects associated with long-term use of NSAAs.

6.6.4.2 Non-steroidal anti-androgen monotherapy

Based on a Cochrane SR [555] comparing NSAA monotherapy to castration (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events. The evidence quality of the studies included in this review was rated as moderate.

6.6.4.3 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [556-558] and two meta-analyses [559, 560], looked at the clinical efficacy of IAD therapy. All of these reviews included eight RCTs of which only three were conducted in patients with exclusively M1 disease. The five remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

So far, the SWOG 9346 [561] is the largest trial conducted in M1b patients. Out of 3,040 selected patients, only 1,535 were randomised based on the inclusion criteria set. This highlights that, at best, only 50% of M1b patients might be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: (HR: 1.1; CI: 0.99-1.23), with the upper limit being above the pre-specified 90% upper limit of 1.2. The pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, inferior survival with IAD cannot be completely ruled out based on this study.

Other trials did not show any survival difference with a HR for OS of 1.04 (0.91-1.19). These reviews and the meta-analyses came to the conclusion that there was no difference in OS or CSS between IAD and continuous androgen deprivation. A recent review of the available phase III trials highlighted the limitations of most trials and suggests a cautious interpretation of the non-inferiority results [562]. None of the trials addressing M1 patients only showed a survival benefit, but there was a trend favouring continuous treatment for OS and PFS. Most of these trials, however, were non-inferiority trials. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side effects, such as hot flushes. In some cohorts the negative impact on sexual function was less pronounced with IAD. Two prospective trials came to the same conclusions [563, 564].

Other possible long-term benefits of IAD include bone protection [565] and a protective effect against metabolic syndrome. This possible protective effect has been challenged recently [566] with an increased risk for thrombotic and ischaemic events, while no benefit was observed for the endocrine, psychiatric, sexual and neurological side effects based on a detailed analysis from the SWOG 9346 trial. Testosterone recovery was observed in most studies [567] leading to intermittent castration. This, as well as the lack of any survival benefit in M1 patients, suggests that this modality must only be considered as an option in a well-informed patient bothered by significant side effects and willing to avoid them.

The PSA threshold at which ADT must be stopped or resumed still needs to be defined in prospective studies [557, 567]. Nevertheless, there is consensus amongst authors on some statements:

- Intermittent androgen deprivation is based on intermittent castration; therefore, only drugs leading to castration are suitable.
- Luteinising-hormone releasing hormone antagonist might be a valid alternative to an agonist.
- The induction cycle cannot be longer than nine months, otherwise testosterone recovery is unlikely.
- Androgen deprivation therapy should be stopped only if patients have fulfilled all of the following criteria:

- well-informed and compliant patient;
- no clinical progression;
- a clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease.
- Strict follow-up is mandatory, with clinical examination every three to six months. The more advanced the disease, the closer the follow-up should be. The same laboratory should be used to assess the PSA level.
- Treatment is resumed when the patient progresses clinically, or has a PSA rising above a pre-determined (empirically set) threshold: usually 10-20 ng/mL in metastatic patients.
- The same treatment is used for at least three to six months.
- Subsequent cycles of treatment are based on the same principles until the first sign of castration resistance becomes apparent.
- The group of patients who will benefit most from IAD still has to be defined but the most important factor seems to be the patient's response to the first cycle of IAD, e.g. the PSA level response [557].

6.6.4.4 Immediate versus deferred androgen deprivation therapy

In symptomatic patients, immediate treatment is mandatory. However, controversy still exists for asymptomatic metastatic patients due to the lack of quality studies. A Cochrane review extracted four good-quality RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [555]. All of these studies were conducted in the pre-PSA era and included patients with advanced PCa, who had received early vs. deferred ADT, either as primary therapy or as adjuvant therapy after RP [568]. No improvement in OS was observed in the M1a/b population, although early ADT significantly reduced disease progression and associated complications.

6.6.5 Hormonal treatment combined with chemotherapy

Three large RCT were conducted [473, 547, 569]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every three weeks) (within three months of ADT initiation). The primary objective in all three studies was OS. The key findings are summarised in Table 6.6.1.

Table 6.6.1: Key findings - Hormonal treatment combined with chemotherapy

Study	Population	n	Med FU (mo)	Median OS (mo)		HR	p-value
				ADT + D	ADT		
Gravis, <i>et al.</i> [569]	M1	385	50	58.9	54.2	1.01 (0.75-1.36)	0.955
ASCO GU 2015 [570]	HV : 47%		82.9	60.9	46.5	0.9 (0.7-1.2)	0.44
Sweeney, <i>et al.</i> [547]	M1 HV: 65%	790	28.9	57.6	44	0.61 (0.47-0.8)	< 0.001
STAMPEDE [473]	M1 [61%]/N+ [15%]/relapse	1,184 /593 (D) 593 (D + ZA)		81	71	0.78 (0.66-0.93)	0.006
	M1 only	725 + 362 (D)		76	NR	0.82 (0.69-0.97)	0.022
				60	45	0.76 (0.62-0.92)	0.005

D = docetaxel; FU = follow-up; HR = hazard ratio; HV = high volume: either visceral metastases or more than four bone metastases, with at least one outside the spine and pelvis; n = number of patients; ZA = zoledronic acid.

In the GETUG 15 trial [569], all patients had newly diagnosed M1 PCa, either primary or after a primary treatment. They were stratified based on previous treatment, and Glass risk factors [545]. In the Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial, the same inclusion criteria applied and patients were stratified according to disease volume; high volume being defined as either presence of visceral metastases or four, or more, bone metastases, with at least one outside the spine and pelvis [547].

STAMPEDE is a multi-arm multi-stage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593 patients), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1, or N1 or having two criteria out of three: T3/4, PSA ≥ 40 ng/mL, Gleason 8-10. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA ≥ 4 ng/mL with a PSA-DT < 6 months, a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [473].

In the three trials toxicity was mainly haematological with around 12-15% Grade 3-4 neutropenia, and 6-12% Grade 3-4 febrile neutropenia. Determination of granulocyte colony-stimulating factor receptor (GCSF) was shown to be helpful and its use should be based on available guidelines [571, 572].

Based on these data, upfront docetaxel combined with ADT should be considered as a new standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug [571]. Docetaxel is used at the standard regimen of 75 mg/sqm combined with steroids premedication, but without prolonged corticotherapy.

6.6.6 **Prostate targeted therapy in newly diagnosed metastatic disease**

Data from the retrospective SEER data-base [573] and the Munich cancer registry [574] suggest an OS and CSS benefit when RP or brachytherapy are added to ADT in newly diagnosed M1 patients. A small prospective experimental cohort of well selected patients responding to six months ADT and with ≤ 3 bone spots confirmed the feasibility and after a median 34 months follow up suggested a better CSS [575]. However, these results must be considered as experimental and deserve prospective trials (already underway) before being adopted in daily practice.

6.6.7 **Metastasis-directed therapy**

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. A recent SR clearly highlighted that at this time this approach must, as yet, be considered as experimental [576].

6.6.8 **Imaging as marker of response in metastatic prostate cancer**

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods (CT or MRI) using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used in bone where response assessment is difficult [577, 578].

Quantitative estimation of tracer uptake at BS can be obtained through automated methods such as the Bone Scan Index [579]. Nonetheless, BS is limited by the so-called 'flare' phenomenon which is defined by the development of new images induced by treatment on a first follow-up scan that actually represent a favourable response on longer observation. Flare is observed within eight-twelve weeks of treatment initiation and can lead to false-positive diagnosis of disease progression. As a result, the Prostate Cancer Clinical Trials Working Group (PCWG) suggested that all patients with at least two new lesions on the first follow-up BS require a confirmatory BS at least six weeks later while the treatment is continued [580]. This means that a management change for primary therapy resistance cannot occur until after at least fourteen weeks of treatment. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. The ability of choline PET/CT to assess response has been assessed in a few studies that showed changes in disease extent and specific uptake values. It is noteworthy that the flare phenomenon can also be observed with choline PET/CT. Magnetic resonance imaging can directly assess the bone marrow and could assess progression based on morphologic criteria or changes in apparent diffusion coefficient. However, a large-scale validation of these criteria has not been performed [577, 578].

In practice, imaging to assess progression leading to treatment change must be limited to a clear progression: RECIST criteria for non-bone lesions; for bone lesions, only BS progression (occurrence of two new hot spots, later confirmed) should be considered. The practical impact of mpMRI in assessing bone progression remains unclear.

6.6.9 **Guidelines for the first-line treatment of metastatic prostate cancer**

Recommendations	LE	GR
Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.	1a	A
Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with chemotherapy.	1b	A
Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial.	3	A
Use castration combined with any local treatment (radiotherapy/surgery) in an investigational setting only.	3	A

6.6.10 **Guidelines for hormonal treatment of metastatic prostate cancer**

Recommendations	LE	GR
In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).	1b	A
In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	1b	A
In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.	1a	A
In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side effects, provided the patient is closely monitored.	2b	B
Anti-androgens		
In M1 patients treated with a luteinising-hormone releasing hormone (LHRH) agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	2a	A
Start anti-androgens used for 'flare-up' prevention on the same day as an LHRH analogue is started or for up to seven days before the first LHRH analogue injection if the patient has symptoms. Treat for four weeks.	3	A
Do not offer anti-androgen monotherapy.	1a	A
Intermittent treatment		
In asymptomatic M1 patients, offer intermittent treatment to highly motivated men, with a major prostate-specific antigen (PSA) response after the induction period.	1b	B
<ul style="list-style-type: none"> In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment. Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment. Resume treatment when the PSA level is > 10-20 ng/mL (or returned to the initial level of < 20 ng/mL). 	4	C
In M1 patients, offer combined treatment with LHRH agonists and a non-steroidal anti-androgen.	1b	A
Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction.	2	B

6.7 Management of prostate cancer in older men**6.7.1 Evaluating health status in senior adults****6.7.1.1 Introduction**

With a median age at diagnosis of 68 years, PCa is common in men aged > 70 years. However, in the USA, the increase in men aged > 65 years being diagnosed will result in an estimated 70% increase in annual diagnosis of PCa by 2030 [581]. A similar increase is expected in Europe [582].

The SEER database shows that 71% of PCa-related deaths occur in men aged ≥ 75 years [583], probably due to the higher incidence of advanced/metastatic disease [584-586].

Despite the high incidence and mortality rates in senior adults, they may be under-treated [587, 588]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease receive curative treatment compared to 88% aged 65-74 [589].

6.7.1.2 Evaluation of life expectancy, comorbidity and health status

In localised disease, > 10 years life expectancy is considered mandatory for any benefit from local treatment. However, comorbidity is more important than age in predicting overall mortality in localised PCa [322]. Besides comorbidities, dependence in daily activities, malnutrition and cognitive impairment are associated with worse survival.

6.7.1.2.1 Comorbidity

Comorbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP [590]. This can be explained by the observations from a study in which patients did not receive active local treatment for their PCa [322]. At ten years, most men with a CCI score > 2 had died from competing causes, irrespective of age or tumour aggressiveness.

Currently, the Cumulative Illness Score Rating-Geriatrics (CISR-G; Table 6.7.1) [591] is the best tool for assessing mortality risk unrelated to PCa [592].

Table 6.7.1: Cumulative Illness Score Rating-Geriatrics (CISR-G)

Cumulative Illness Rating Scale	Rating strategy
0	None
1	Mild (or past significant problem)
2	Moderate (moderate disability or morbidity, requires first-line therapy)
3	Severe (constant significant disability/uncontrollable chronic problems)
4	Extremely severe (immediate treatment required/end organ failure/severe impairment in function)
	Score
Heart	
Vascular	
Respiratory	
Eyes, ears, nose, throat and larynx	
Upper GI	
Lower GI	
Hepatic	
Renal	
Genitourinary	
Musculoskeletal/integument	
Neurological	
Endocrine/metabolic	
Psychiatric illness	
Total score	

Patients are considered fit if they have no Grade 3 score

Frail: one or two Grade 3 scores

Disabled: > 2 Grade 3, or any Grade 4 scores

Too sick: multiple Grade 4 scores

6.7.1.2.2 Dependence in daily activities

The level of dependence in daily activities influences survival in senior adults [593-595]. The Activities of Daily Living (ADL) scale rates accomplishment of basic activities of daily living, while the Instrumental Activities of Daily Living (IADL) scale rates activities requiring higher cognition and judgement.

6.7.1.2.3 Malnutrition

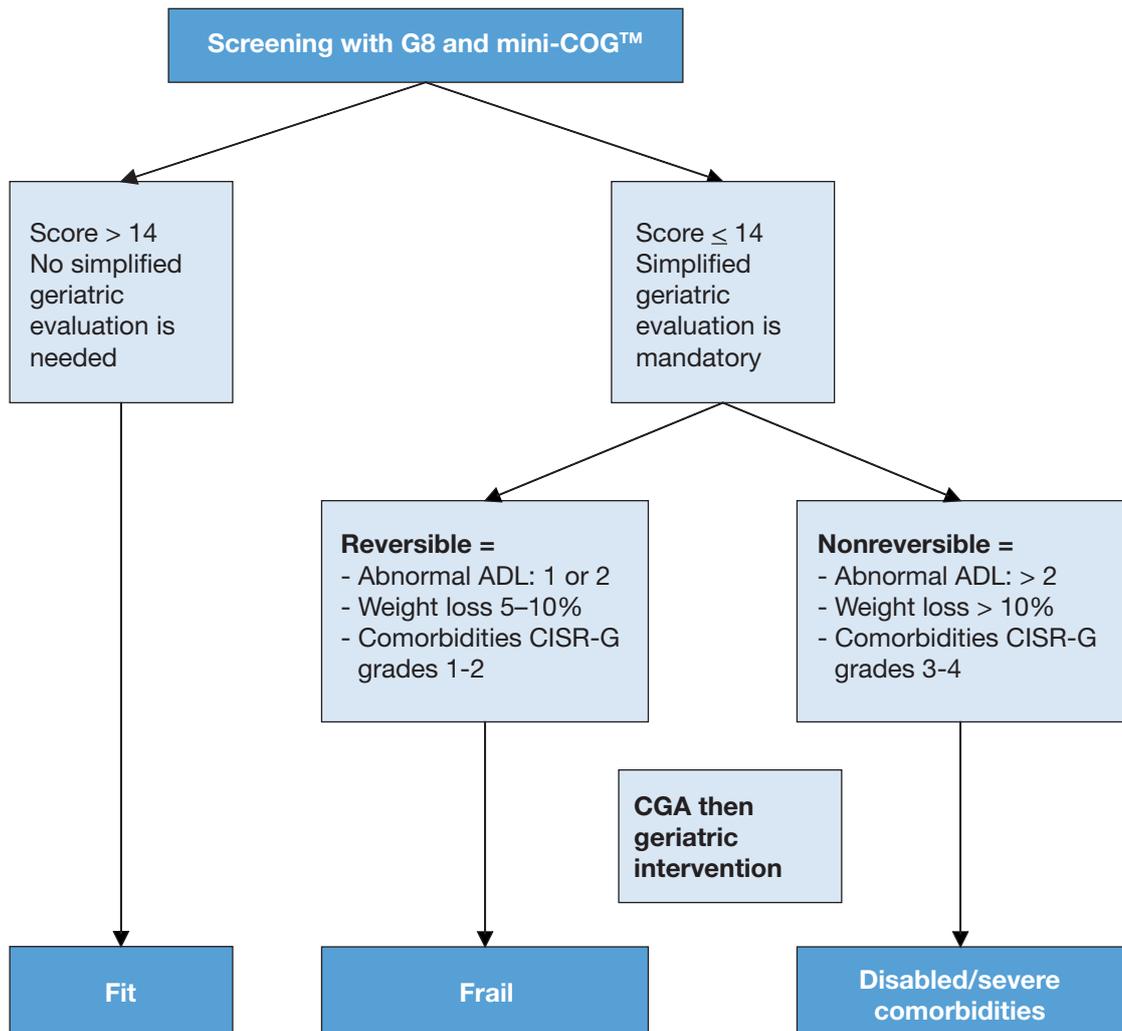
Malnutrition is associated with increased mortality in senior patients [596]. Nutritional status can be estimated from body weight during the previous three months:

- Good nutritional status < 5% weight loss;
- Risk of malnutrition: 5-10% weight loss;
- Severe malnutrition: > 10% weight loss.

6.7.1.2.4 Cognitive impairment

Cognitive impairment is associated with increased mortality risk in senior adults [597]. In patients undergoing major elective surgery, there is an association between baseline cognitive impairment and long-term post-operative complications and mortality [598]. Intervention is unlikely to reverse cognitive impairment, except in depression [599]. The mini-COG is the best available tool to evaluate cognitive function in order to assess the patient's ability to make an informed decision [600].

Figure 6.7.1: Decision tree to determine patient health status* [599]



*Reproduced with permission of Elsevier, from Droz J-P, et al. *Eur Urol* 2017 (prior to press) [599].
 Mini-COG™ = mini-COG™ cognitive test; ADL = activities of daily living; CIRS-G = cumulative illness rating score-geriatrics; CGA = comprehensive geriatric assessment.

6.7.1.2.5 Baseline screening using the G8 screening tool

The International Society of Geriatric Oncology (SIOG) PCa Working Group (PCWG) recommends that treatment for senior adults should be based on a systematic evaluation of health status [599].

The G8 (Geriatric 8) health status screening tool is described in Table 6.7.2, the Karnofsky and ECOG Scores in Table 6.7.3 [601].

Table 6.7.2: G8 screening tool (Adapted from [602])

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
E	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
F	BMI? (weight in kg)/(height in m ²)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
H	Takes more than three prescription drugs per day?	0 = yes
		1 = no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
	Age	0: > 85
		1: 80-85
		2: < 80
	Total score	0-17

A G8 score > 14 shows that patients should receive the same treatment as younger patients. Patients with score $G8 \leq 14$ should undergo a full geriatric evaluation, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [602]. Patients with reversible impairment (frail patients) should be treated according to the EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines. Patients with irreversible impairment (disabled patients) should receive adapted treatment [599].

Table 6.7.3: Performance Scales - Karnofsky & ECOG Scores [601]

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints.	100	0	Fully active, able to carry on all pre-disease performance without restriction.
Able to carry on normal activities. Minor signs or symptoms of disease.	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Normal activity with effort.	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Care for self. Unable to carry on normal activity or to do active work.	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires occasional assistance, but able to care for most of his needs.	60	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires considerable assistance and frequent medical care.	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
Disabled. Requires special care and assistance.	40	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
Severely disabled. Hospitalisation indicated though death non-imminent.	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
Very sick. Hospitalisation necessary. Active supportive treatment necessary.	20	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
Moribund.	10	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

6.7.1.2.6 Conclusions

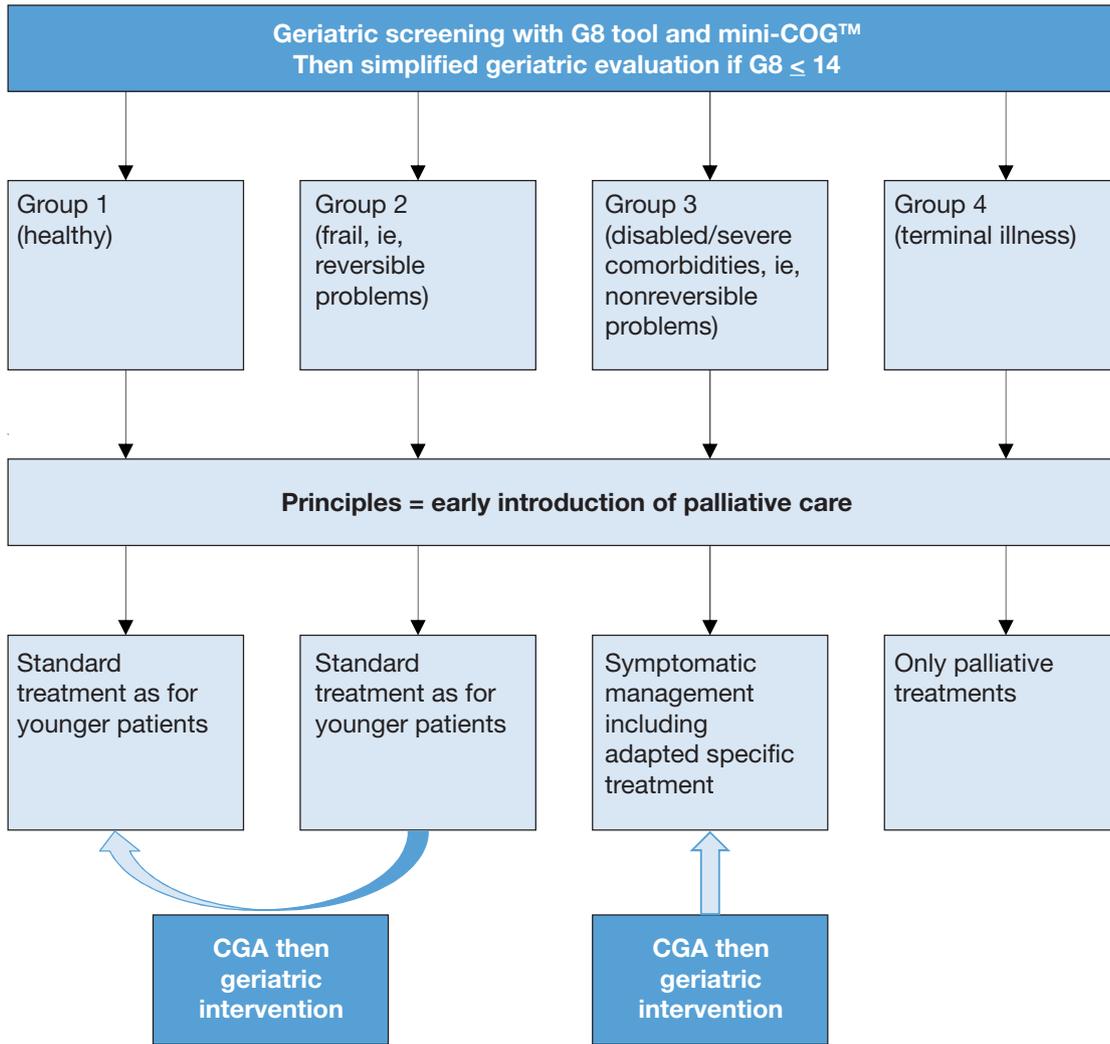
Systematic assessment, using the G8 tool, is recommended by the SIOG PCWG [599]. Patients with G8 score < 14 should undergo complete geriatric assessment to evaluate reversibility of any impairments [599].

Senior adults can be classified into one of four groups regarding health status based on G8 score > 14 (patient considered fit), or score < 14 (patient considered frail or disabled). The treatment policy is then:

- fit or healthy older men should receive standard treatment;
- frail patients may receive standard treatment after resolution of any geriatric problems;
- disabled patients (i.e. non-reversible problems) should receive adapted treatment;
- patients who are too sick with terminal illness should receive only palliative treatment [599].

After resolution of reversible impairments, a similar urological approach should be carried out in fit or frail patients [1, 2]. Older men with PCa should be managed according to their individual health status, which is directed by the presence of any associated comorbidity and not age.

Figure 6.7.2: Decision-making based on health status assessment* [599]



*Reproduced with permission of Elsevier, from Droz J-P, et al. Eur Urol 2017 (prior to press) [599].
Mini-COG™ = mini-COG™ cognitive test; ADL = activities of daily living; CIRS-G = cumulative illness rating score-geriatrics; CGA = comprehensive geriatric assessment.

6.7.1.3 Guidelines for the evaluation of health status in elderly men

Recommendations for assessment	LE	GR
Perform systematic health status screening in senior adults with localised PCa.	1b	A
Use the G8 screening tool for health status screening.	2a	A
Perform a full specialist geriatric evaluation in patients with G8 score ≤ 14.	2a	A
Treatment options for senior adults according to their health status: 1. offer standard treatment to fit or healthy older men; 2. offer standard treatment to frail patients (reversible impairment) after resolution of geriatric problems; 3. offer adapted treatment to disabled patients (irreversible impairment); 4. offer only symptomatic palliative treatment to patients who are too sick with terminal illness.	3	B

6.7.2 Specific aspects of PCa treatment in older men

6.7.2.1 Localised PCa

6.7.2.1.1 Deferred treatment (active surveillance, watchful waiting)

Deferred treatment is addressed in Section 6.1. Active treatment mostly benefits patients with intermediate- or high-risk disease and longest expected survival. A recent study assessed the effect of age, health status and patient preferences on outcomes of surgery vs. AS for low-risk PCa. As expected, older age and worse

baseline health status were associated with a smaller benefit in PCSM and life expectancy with surgery, and increased incremental years with treatment side effects. Older men and men in poor health were likely to have better quality-adjusted life expectancy with AS [603].

6.7.2.1.2 Radical prostatectomy

Senior adults (aged ≥ 75 years) are more likely to present with very advanced disease and have a greater risk of death from PCa, despite higher death rates from competing causes [584]. In the most recent update of the SPCG-4 study, randomising patients with localised PCa to RP vs. WW, the benefit of surgery with respect to death from PCa was largest in men < 65 years of age (RR, 0.45). However, RP was associated with a reduced risk of metastases and use of androgen deprivation therapy among older men (RR: 0.68 and 0.60, respectively) [333]. Risk of short-term complications after RP is related more to comorbidity severity than age. Conversely, risk of long-term incontinence is influenced more by increasing age [604, 605].

6.7.2.1.3 External beam radiotherapy

External beam radiotherapy and RP have similar cancer control and treatment-related comorbidity, regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [606].

Cardiac status should be assessed because ADT in patients with pre-existing heart conditions is associated with increased morbidity and mortality. Patients with moderate-to-severe comorbidities might not have a significant survival-benefit when combining ADT with EBRT [454].

6.7.2.1.4 Minimally invasive therapies

Minimally invasive energy-ablative therapies are being developed rapidly, but there is still a lack of evidence to support their use.

6.7.2.1.5 Androgen deprivation therapy

In patients with non-metastatic localised PCa not suitable for curative treatment, immediate ADT should be used only in patients requiring symptom palliation. In locally advanced T3-T4 disease, immediate ADT may benefit patients with PSA > 50 ng/mL and PSA-DT < 12 months [328, 607].

6.7.2.2 Advanced PCa

6.7.2.2.1 Hormone-naïve metastatic PCa

Androgen deprivation therapy is the first-line treatment in hormone-sensitive metastatic PCa. The SIOG PCWG recommends evaluation of baseline bone mineral density and prevention of osteoporosis by calcium and vitamin D supplements [599].

Routine bisphosphonates or denosumab to prevent skeletal complications in ADT is not recommended, unless there is a risk of fracture [608].

6.7.2.2.2 Metastatic CRPC

In metastatic CRPC, docetaxel is standard in fit and frail older men [609], with comparable response and tolerance to younger patients [610]. Tolerability has not been specifically studied in disabled older men. In elderly and disabled patients, granulocyte colony-stimulating factor prophylaxis should be considered.

Cabazitaxel, abiraterone acetate, enzalutamide, and sipuleucel-T increase survival in chemotherapy-treated and chemotherapy-naïve senior adults [611-617].

Palliative treatment includes surgery, radiopharmaceuticals, EBRT, and medical treatment for pain and symptoms.

6.7.3 Guidelines for the treatment of senior adults (> 70 years of age)

Recommendations for assessment	GR
Perform systematic health status screening in senior adults with localised PCa.	A
Use the G8 screening tool for health status screening.	A
Perform a full specialist geriatric evaluation in patients with G8 score ≤ 14 .	A
Treatment options for senior adults according to their health status: 1. Offer standard treatment to fit or healthy older men; 2. Offer standard treatment to frail patients (reversible impairment) after resolution of geriatric problems; 3. Offer adapted treatment to disabled patients (irreversible impairment); 4. Offer only symptomatic palliative treatment to patients who are too sick with terminal illness.	B

Recommendations for treatment	LE	GR
Localised disease		
Offer standard treatment to fit and frail senior adults (after status optimisation) with a life expectancy > 10 years.	2b	A
Offer individualised treatment based on life expectancy, symptoms and risk factors to senior adults with a life expectancy < 10 years.	2b	A
In disabled or 'too-sick' senior adults, offer immediate androgen deprivation therapy only for symptom palliation.	1b	A
Offer minimally invasive energy-ablative therapies only to selected fit and frail senior adults with intermediate-risk disease.	3	B
Advanced disease (locally advanced/metastatic disease)		
Evaluate bone mineral status and prevent osteoporosis-related fractures in senior adults.	2b	A
Offer new chemotherapeutic and hormonal agents to fit and frail adults.	1b	B

6.8 Summary of guidelines for the primary treatment of prostate cancer

Table 6.8.1: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	Intermediate-risk	High-risk	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS cT3-4 or cN+ any ISUP grade
Localised			Locally advanced

PSA = prostate-specific antigen.

Guidelines overview - Primary treatment of PCa

Primary treatment of prostate cancer - general recommendations	GR
Discuss several treatment modalities (active surveillance [AS], surgery and radiotherapy) with patients suitable for such treatments.	A*
In patients who are surgical candidates for radical prostatectomy (RP), discuss all approaches (i.e. open, laparoscopic or robotic) as acceptable treatment options since none have clearly shown superiority in terms of functional or oncological results.	A
Offer external beam radiotherapy (EBRT) to all risk groups of non-metastatic PCa.	A
Offer intensity-modulated radiation therapy (IMRT) for definitive treatment of PCa by EBRT.	A
Moderate hypofractionation (HFX) with IMRT including image-guided radiation therapy (IGRT) to the prostate can only be offered to carefully selected patients with localised disease.	A
Moderate HFX should adhere to radiotherapy-protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.	A

Recommendations	GR
Low-risk PCa	
Active surveillance	
Offer active surveillance (AS) to patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, prostate-specific antigen (PSA) ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	A
Base follow up on digital rectal examination (DRE), PSA and repeated biopsies.	A
Counsel patients about the possibility of needing further treatment in the future.	A
Radical prostatectomy	
Offer both radical prostatectomy (RP) and radiotherapy (RT) in patients with low- and intermediate-risk PCa and a life expectancy > 10 years.	A
Do not perform a lymph node dissection (LND) in low-risk PCa.	A

Radiotherapy	In low-risk PCa, use a total dose of 74 to 78 Gy for external beam radiotherapy (EBRT).	A
	In patients with low-risk PCa, without a previous transurethral resection of the prostate (TURP) and with a good International Prostate Symptom Score (IPSS) and a prostate volume < 50 mL, offer low-dose-rate (LDR) brachytherapy.	A
Cryotherapy, HIFU	Only offer cryotherapy and high-intensity focused ultrasound (HIFU) within a clinical trial setting. The lack of long-term efficacy compared to standard modality must be discussed with patients.	A
Focal treatment	Do not offer focal therapy of PCa as a therapeutic alternative outside clinical trials.	A
Androgen suppression	Unsuitable.	A
Watchful waiting	Offer watchful waiting (WW) to patients not eligible for local curative treatment and with a short life expectancy.	A
Intermediate-risk PCa		
Active surveillance	Not an option.	A
Radical prostatectomy	Offer both RP and RT in patients with low- and intermediate-risk disease and a life expectancy > 10 years.	A
	Offer nerve-sparing surgery in patients with a low risk of extracapsular disease (refer to nomograms).	B
	Use multiparametric magnetic resonance imaging (mpMRI) as a decision tool to select patients for nerve-sparing procedures.	B
	Perform an extended LND (eLND) if the estimated risk for positive lymph nodes (LNs) exceeds 5%.	B
	Do not perform a limited LND.	A
	In patients with pT3,N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it at least improves biochemical-free survival.	A
	Inform patients with pT3,N0M0 PCa and an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A
	Do not offer adjuvant hormonal therapy (HT) after RP for pN0 disease.	A
Radiotherapy	In intermediate-risk PCa use a total dose of 76-78 Gy, in combination with short-term androgen deprivation therapy (ADT) (four to six months).	A
	In selected intermediate-risk patients, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, offer LDR brachytherapy.	A
Androgen suppression monotherapy	No place in asymptomatic patients.	A
Watchful waiting	Offer WW to patients not eligible for local curative treatment and with a short life expectancy.	A
High-risk PCa		
Watchful waiting	High risk localised: Offer WW to patients not eligible for local curative treatment and with a short life expectancy.	A
	High risk locally advanced: In locally advanced M0 patients unwilling or unable to receive any form of local treatment, offer a deferred treatment policy to asymptomatic patients with a PSA-DT > 12 months and a PSA < 50 ng/mL and non-poorly differentiated tumour.	A
Active surveillance	Not appropriate.	A
Radical prostatectomy	Do not offer neoadjuvant hormonal therapy before RP.	A
	Offer RP in selected patients with locally advanced (cT3a) disease and a life expectancy > 10 years only as part of multi-modal therapy	A
	Offer nerve-sparing surgery in patients with a low risk of extracapsular disease (refer to nomograms).	A
	Perform an eLND in high-risk PCa.	A

	High risk localised: Offer RP in patients with high-risk localised PCa and a life expectancy of > 10 years only as part of multi-modal therapy.	A
	In high-risk disease, use mpMRI as a decision-making tool to select patients for nerve-sparing procedures.	B
	High risk locally advanced: Offer RP in highly selected patients with (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.	C
	In patients with pT3,N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it at least improves biochemical-free survival.	A
	Inform patients with pT3,N0M0 PCa and an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases.	A
Radiotherapy	Inform patients with an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases (see Section 6.9.5.1).	A
	In patients with high-risk localised PCa and locally advanced cN0 PCa, use EBRT to a dose of 76-78 Gy, or combined EBRT with brachytherapy boost (either high-dose rate [HDR] or LDR). Radiotherapy should be given in combination with long-term ADT (two to three years).	A
	In patients with locally advanced cN0 PCa, offer RT in combination with long-term ADT (two to three years is recommended).	A
Androgen suppression monotherapy	Reserved for those patients unwilling or unable to receive any form of local treatment and that are either symptomatic or asymptomatic with a PSA-DT < 12 months and a PSA > 50 ng/mL and a poorly differentiated tumour.	A
	Do not offer ADT to patients with a PSA-DT > 12 months	A
N1 patients		
cN1	In patients with cN+ PCa, offer pelvic external beam irradiation in combination with immediate long-term ADT.	B
pN1 after extended lymph node dissection (eLND)	Offer adjuvant ADT for node-positive (pN+).	B
	Offer adjuvant ADT with additional radiotherapy.	A
	Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	B
Metastatic PCa		
Active surveillance	Unsuitable.	A
Radical prostatectomy	Unsuitable outside clinical trial.	A
Radiotherapy to the prostate	Unsuitable outside clinical trial.	A
Androgen suppression	Offer surgical or medical castration (luteinising-hormone-releasing hormone [LHRH] agonist or antagonist) as androgen deprivation therapy.	A
	Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.	A
	Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with chemotherapy.	A
	Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial.	A
	In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, urethral obstruction, extra-skeletal metastases).	A
	In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.	A
	In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side effects, provided the patient is closely monitored.	B

	Do not routinely offer ADT to asymptomatic men with biochemical recurrence.	A
	In M1 patients treated with an LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	A
	Start anti-androgens used for 'flare-up' prevention on the same day as an LHRH analogue is started or for up to seven days before the first LHRH analogue injection if the patient has symptoms). Treat for four weeks.	A
	Do not offer anti-androgen monotherapy in M1 patients.	A
	Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction.	B
	In asymptomatic M1 patients, offer intermittent treatment to highly motivated patients, with a major PSA response after the induction period.	B
	In M1 patients follow the schedules used in published clinical trials on timing of intermittent treatment. Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment. Resume treatment when the PSA level is > 10-20 ng/mL (or back to the original level, if < 20 ng/mL).	C

Guidelines for the treatment of senior adults (> 70 years of age)

Recommendations for assessment	GR
Perform systematic health status screening in senior adults with localised PCa.	A
Use the G8 screening tool for health status screening.	A
Perform a full specialist geriatric evaluation in patients with G8 score ≤ 14.	A
Treatment options for senior adults according to their health status: 1. offer standard treatment to fit or healthy older men; 2. offer standard treatment to frail patients (reversible impairment) after resolution of geriatric problems; 3. offer adapted treatment to disabled patients (irreversible impairment); 4. offer only symptomatic palliative treatment to patients who are too sick with terminal illness	B

Recommendations for treatment	LE	GR
Localised disease		
Offer standard treatment to fit and frail senior adults (after status optimisation) with a life expectancy > 10 years.	2b	A
Offer individualised treatment based on life expectancy, symptoms and risk factors to senior adults with a life expectancy < 10 years.	2b	A
In disabled or 'too-sick' senior adults, offer immediate androgen deprivation therapy only for symptom palliation.	1b	A
Offer minimally invasive energy-ablative therapies only to selected fit and frail senior adults with intermediate-risk disease.	3	B
Advanced disease (locally advanced/metastatic disease)		
Evaluate bone mineral status and prevent osteoporosis-related fractures in senior adults.	2b	A
Offer new chemotherapeutic and hormonal agents to fit and frail adults.	1b	B

6.9 Treatment - Management of PSA-only recurrence after treatment with curative intent

6.9.1 Background

Between 27% and 53% of all patients undergoing RP or RT develop PSA-recurrence (see Sections 6.2 and 6.3). Whilst a rising PSA level universally precedes metastatic progression, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily lead to clinically apparent metastatic disease. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may never affect their OS or QoL. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

6.9.2 Definitions

6.9.2.1 Definition of biochemical recurrence

The PSA level that defines treatment failure depends on the primary treatment. After RP, recurrent cancer is defined by two consecutive PSA values of > 0.2 ng/mL and rising [618-620].

After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of $> 80\%$) is any PSA increase ≥ 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir [621].

Importantly, patients with PSA-recurrence after RP or primary RT have different risks of subsequent symptomatic metastatic disease. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments.

6.9.3 Natural history of biochemical recurrence

Once a PSA relapse has been diagnosed, it is important to determine, as far as possible, whether the recurrence has developed at local or distant sites. The risk of subsequent metastases and PCSM may be predicted by the initial clinical and pathologic factors (e.g. T-category, PSA, Gleason score) and PSA kinetics (PSA-DT and interval to PSA failure).

6.9.3.1 Post-radical prostatectomy biochemical recurrence

Not all patients with BCR after RP will develop clinical recurrences. In two studies of 1,997 and 2,400 men treated by RP, only 23-34% of those with BCR develop a clinical recurrence and 6% died of PCa [378, 622].

Several studies have attempted to identify risk factors for metastases and PCSM in patients experiencing PSA-only recurrence following RP. A PSA-DT < 3 months, SVI (pT3b), specimen Gleason score 8-10, or time to PSA-recurrence < 3 years indicate a high risk of metastases and PCSM. Conversely, a PSA-recurrence > 3 years following surgery, specimen Gleason score < 7 , pathologic organ-confined disease or limited extracapsular extension (pT3a), and PSA-DT > 12 months indicate a low risk of metastases and PCSM [623-626]. Patients in the low-risk subgroup typically respond very well to SRT with a high probability of PSA being undetectable [627]. However, it must be stressed that most patients within the low-risk subgroup have an excellent outcome even without any salvage treatment. Patients within the high-risk subgroup need early and aggressive salvage treatment [628]. Trock *et al.* demonstrated that SRT was associated with a significant three-fold increase in PCa-specific survival relative to those who received no salvage treatment. The increase in PCa-specific survival associated with SRT was limited to men with a PSA-DT of < 6 months and remained after adjustment for pathological stage and other established prognostic factors. Salvage RT initiated > 2 years after recurrence provided no significant increase in PCa-specific survival [628].

6.9.3.2 Post-radiotherapy biochemical recurrence

In patients experiencing PSA-recurrence after RT, PSA-DT < 3 months, time to biochemical progression < 3 years, biopsy Gleason score 8-10 or clinical stage cT3b-T4 also indicate a high risk of metastases and PCSM. Conversely, PSA-DT > 15 months, biopsy Gleason score < 7 , clinical stage $< cT3a$ and time to BCR > 3 years indicate a low risk of metastases and PCSM [625, 629, 630].

Zumsteg *et al.* have designed a risk score to further subdivide patients who develop PSA recurrence following RT. Those with > 2 high-risk factors (PSA-DT < 3 months, time to BCR < 3 years, biopsy Gleason score 8-10 and clinical stage cT3b-T4) have an increased risk of developing metastases and PCSM as compared to those with 0 or 1 risk factor [630].

6.9.4 Assessment of metastases

6.9.4.1 Bone scan and abdominopelvic computed tomography

Biochemical recurrence after RP or RT precedes clinical metastases by seven to eight years on average, and consequentially the diagnostic yield of common imaging techniques is poor in asymptomatic patients [631]. In men with PSA-only relapse after RP, the probability of a positive BS is $< 5\%$, when the PSA level is < 7 ng/mL [632, 633].

Only 11-14% of patients with BCR after RP have a positive CT and rarely in situations when salvage treatment might be considered [632]. In a series of 132 men with BCR after RP, the mean PSA level and PSA velocity associated with a positive CT was 27.4 ng/mL and 1.8 ng/mL/month, respectively [634]. Therefore, bone scan and abdominopelvic CT should only be considered in patients with BCR after RP who have a high baseline PSA (> 10 ng/mL) or high PSA kinetics (PSA-DT < 6 months or PSA velocity > 0.5 ng/mL/month) or in patients with symptoms of bone disease [632, 634].

6.9.4.2 Choline PET/CT

In two different meta-analyses, the combined sensitivities and specificities of choline PET/CT for all sites of recurrence in patients with BCR were 86-89% and 89-93%, respectively [635, 636]. Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on BS [637] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative BS [638]. The specificity of choline PET/CT is also higher than BS with less false-positive and indeterminate findings [257]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.4.1.)

Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [249, 639-641]. In patients with BCR after RP, PET/CT detection rates are only 5-24% when the PSA level is < 1 ng/mL, but rises to 67-100% when the PSA level is > 5 ng/mL. In a meta-analysis, choline PET/CT detection rates were 65% (95% CI: 58%-71%) when the PSA-DT was < 6 months, and were 71% (95% CI: 66%-76%) and 77% (95% CI: 71%-82%) when the PSA velocity was > 1 and > 2 ng/mL/year, respectively [639].

Despite these limitations, choline PET/CT may change medical management in 18-48% of patients with BCR after primary treatment [642-644]. In a retrospective bi-centric study of 150 patients, 14 of the 55 (25.5%) patients scheduled for palliative treatment were switched to salvage therapy based on choline PET/CT results. Salvage therapy induced a complete biochemical response in 35.7% of these patients at the end of a median follow-up of 18.3 months (range, 10-48 months) [644] suggesting it continues to miss small volume metastasis. In patients not considered fit enough for curative salvage treatments choline PET/CT should be avoided.

After RP, the optimal PSA cut-off level for choline PET/CT analysis seems to be between 1 and 2 ng/mL. Choline PET/CT detection rate was 26% in patients showing PSA < 1 ng/mL but raised up to 44% in the population with PSA values between 1 and 2 (moreover 37% of them were oligo-metastatic) [645]. It has been suggested that a PSA-DT < 6 months and a PSA velocity > 2 ng/mL/year might also select men in whom choline PET/CT could be recommended [646].

After RT, the PSA cut-off level is unclear due to the lack of sufficient data and because the PSA level is more difficult to interpret due to the “physiological” amount of measurable PSA produced by the non-tumoural prostate [640]. In a study of 46 patients with PSA relapse after RT or brachytherapy, the choline PET/CT detection rate was 54.5%, 81%, 89% and 100% when the PSA level was 1-2 ng/mL, 2-4 ng/mL, 4-6 ng/mL and > 6 ng/mL, respectively [647]. In another study of 140 patients the choline PET/CT detection rate was not influenced by the PSA level, but only by PSA kinetics [648].

6.9.4.3 Other radionuclide techniques

¹⁸F-Fluoride PET and PET/CT have a higher sensitivity than BS in detecting bone metastases [649]. However, ¹⁸F-Fluoride PET and PET/CT is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [650].

⁶⁸Ga-PSMA PET/CT has shown promising potential in patients with BCR. Detection rates of 58% and 76% have been reported for PSA ranges of 0.2-1 and 1-2 ng/mL, respectively [256]. This suggests that ⁶⁸Ga-PSMA is substantially more sensitive at low PSA levels than choline PET/CT. Two head-to-head comparisons confirmed this finding [651, 652]. However, studies incorporated varying proportions of initial therapy (RP or RT) and a majority of studies included patients on current ADT. Further prospective studies on homogeneous populations are needed to better define the role of ⁶⁸Ga-PSMA PET/CT in patients with BCR. Therefore it cannot yet be considered as a standard evaluation tool. However, in case local salvage treatment is planned and ⁶⁸Ga-PSMA PET/CT is available, it should be considered as a valuable assessment option.

6.9.4.4 Whole-body and axial magnetic resonance imaging

Little is known regarding the accuracy of whole-body or axial MRI in patients with BCR after RP or RT [653]. Therefore, the role of these techniques in detecting occult bone or LN metastases in the case of BCR remains to be assessed.

6.9.4.5 Assessment of local recurrences

6.9.4.5.1 Local recurrence after radical prostatectomy

The precise localisation of the local recurrence by imaging techniques is needed only if the localisation could change treatment planning. Transrectal US is neither sensitive nor specific in detecting local recurrences after RP. Even with TRUS guidance, the sensitivity of anastomotic biopsies remains low: 40-71% for PSA levels > 1 ng/mL and 14-45% for PSA levels < 1 ng/mL [631].

Choline PET/CT can detect local recurrences, but is less sensitive than MRI [654] and although ⁶⁸Ga-PSMA PET/CT has improved sensitivity at low PSA levels, it is still unknown if it can reliably detect local

recurrences in the prostate bed, an area that is frequently obscured by tracer excretion in the bladder [655].

Several studies have reported promising results in the detection of local recurrences using MRI, particularly dynamic contrast-enhanced MRI which showed sensitivities and specificities of 76-90% and 82-100%, respectively [656-659]. However, the mean PSA level in these studies was 0.7-1.9 ng/mL, which is higher than the 0.5 ng/mL threshold usually used for salvage therapy. Two studies evaluated mpMRI in patients with a PSA level < 0.5 ng/mL. One found a sensitivity of only 13% in men with PSA level < 0.3 ng/mL [660], while the other reported a sensitivity of 86% in patients with a PSA level < 0.4 ng/mL [661]. It remains to be seen whether MRI can correctly detect local recurrences in patients with a PSA level < 0.5 ng/mL in order to allow a stereotaxic boost to the recurrence site during SRT. Therefore, SRT is usually decided on the basis of BCR, without histological proof of the local recurrence. The dose delivered to the prostatic bed also tends to be uniform as it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Thus, most patients undergo SRT without local imaging.

6.9.4.5.2 Local recurrence after radiation therapy

In patients with BCR after RT, the biopsy status is a major predictor of outcome, provided the biopsies are obtained 18-24 months after treatment. Given the morbidity of local salvage options, it is thus mandatory to obtain histological proof of the local recurrence before treating the patient [631] especially if a local salvage curative treatment is considered.

Transrectal US is not reliable in depicting local recurrences after RT. In contrast, mpMRI has yielded excellent results [631, 662-664] and can be used for biopsy targeting and guiding local salvage treatment. Detection of recurrent cancer is also feasible with choline PET/CT [648], and a nomogram able to predict the probability of extra pelvic disease has been proposed [665]. It is also too soon to know if ⁶⁸Ga-PSMA PET/CT could play a role in the detection of local recurrences after RT [256].

6.9.4.6 Guidelines for imaging in patients with biochemical recurrence

Prostate-specific antigen (PSA) recurrence after radical prostatectomy	LE	GR
PSA < 1 ng/mL: no imaging is recommended.	3	A
PSA ≥ 1 ng/mL: positron emission tomography (PET)/computed tomography (CT) imaging is recommended using choline or prostate-specific membrane antigen (PMSA).	2b	A
Perform bone scan and/or abdominopelvic CT only in patients with PSA > 10 ng/mL, or with adverse PSA kinetics (PSA-doubling time (DT) < 6 months, PSA velocity > 0.5 ng/mL/month).	3	A
PSA recurrence after radiotherapy		
Perform prostate multiparametric magnetic resonance imaging (mpMRI) only in patients who are considered candidates for local salvage therapy, use mpMRI to localise abnormal areas and guide biopsies.	3	B
Choline PET/CT imaging is recommended to rule out lymph nodes or distant metastases in patients fit enough for curative salvage treatment.	2b	B
Perform bone scan and/or abdominopelvic CT only in patients with PSA > 10 ng/mL, or with adverse PSA kinetics (PSA-DT < 6 months, PSA velocity > 0.5 ng/mL/month).	3	A

6.9.5 Treatment of PSA-only recurrences

The timing and mode of treatment for PSA-only recurrences after RP or RT are still controversial.

After RP, the therapeutic options are:

- radiotherapy at least to the prostatic bed;
- (complete) androgen deprivation;
- intermittent androgen deprivation;
- observation.

After RT, the therapeutic options are:

- salvage RP;
- HIFU
- cryotherapy;
- brachytherapy;
- androgen deprivation;
- observation.

6.9.5.1 Radiotherapy (salvage radiotherapy - with or without androgen-deprivation therapy for PSA-only recurrence after radical prostatectomy)

Early SRT provides a possibility of cure for patients with an increasing or persistent PSA after RP. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [505, 666-668], providing patients with a ~80% chance of being progression-free five years later [506]. A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n = 397) or SRT alone (n = 160) within two years of BCR, showed that salvage RT was associated with a three-fold increase in PCa-specific survival relative to those who received no salvage treatment (p < 0.001). Salvage RT has also been effective in patients with a short PSA-DT [628]. Despite the indication for salvage RT, a “wait and see” strategy is an option in patients with a long PSA-DT of > 12 months [622]. For an overview see Table 6.9.1.

Table 6.9.1: Selected studies on post-prostatectomy salvage radiotherapy, sorted by pre-salvage radiotherapy PSA level*

Reference	n	HT (%)	pre-SRT PSA (ng/mL) median	Median dose (Gy)	bNED/PFS (yr)	5-yr results
Siegmann, <i>et al.</i> 2011 [669]	301	0	0.28	66.6/70.2	74% (2)	55% vs. 88% @ 66.6 vs. 70.2 Gy
Wiegel, <i>et al.</i> 2009 [506]	162	0	0.33	66.6	54% (3.5)	60% vs. 33% @ PSA ≤ 0.5 vs. > 0.5
Goenka, <i>et al.</i> 2011 [670]	285	31	0.4	> 70 (72%)	37% (7)	39%
Cremers, <i>et al.</i> 2010 [671]	197	0	0.59	63 /2.25 frct. (88%)	59% (5)	
Bernard, <i>et al.</i> 2010 [672]	364	0	0.6	64.8	50% (5)	
Buskirk, <i>et al.</i> 2006 [673]	368	15	0.7	64.8	46% (5)	63% vs. 51% @ PSA < 0.5 vs. 0.5 - 1.0
Pazona, <i>et al.</i> 2005 [674]	223	4.5	0.8	63	40/25% (5/10)	42% vs. 30% @ < 1.3 vs. ≥ 1.3
Pisansky, <i>et al.</i> 2000 [675]	166	4	0.9	64	46% (5)	61% vs. 36% @ PSA ≤ 1 vs. > 1
Soto, <i>et al.</i> 2012 [676]	441	24	< 1 (58%)	68	63/55% (3) HT/no HT	44/40% HT/no HT
Stephenson, <i>et al.</i> 2007 [505]	1,540	14	1.1	64.8	32% (6)	37%

* Hormone suppression treatment (HT) can influence the outcome ‘biochemically no evidence of disease (bNED)’ or ‘progression-free survival’ (PFS). Therefore, data sets without HT are highlighted. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.

bNED/PFS = biochemically no evidence of disease/progression-free survival; HT = hormone suppression treatment; n = number of patients; SRT = salvage radiotherapy.

Addition of androgen deprivation to SRT improves outcomes. The Radiation Therapy Oncology Group RTOG 96-01 comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) for 24 months in the post-operative setting reported improved overall all survival (82% vs 78% at ten years) [677]. The investigators concluded that 24 months of HT also, significantly reduces metastatic disease, reduces death from CaP (from 7.5% to 2.3%, NNT = 17), reduced overall death (from 22% to 18%) and reduced tumour progression. They found that toxicity was similar in both arms, and that gynaecomastia was extremely common in the bicalutamide group. The GETUG-AFU 16 study [678] confirmed improved bPFS and clinical progression at five years when combining six months of goserelin with SRT, but survival remained unchanged.

6.9.5.1.1 Dose and toxicity

The optimal SRT dose has not been well defined. It should be at least 66 Gy to the prostatic fossa (plus/minus the bed of the seminal vesicles dependent upon the pathological stage at RP) [666]. Similarly, a joint AUA/ASTRO Guideline Panel regarded 64-65 Gy as the minimum dose that should be delivered post-RP [679]. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control

at three to five years [672]. In a SR, the pre-salvage RT PSA level and SRT- dose were correlated with BCR, showing that the relapse-free survival decreased by 2.6% per 0.1 ng/mL PSA and improved by 2% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA level [666, 680, 681]. However, with dose escalation (72 Gy) or up to a median of 76 Gy, the rate of severe side effects especially for the genitourinary system clearly increases, even with newer planning and treatment techniques [682, 683]. Of note, compared with 3D-CRT, IMRT was associated with a reduction in Grade 2 GI toxicity from 10.2 to 1.9% ($p = 0.02$), while RT technique had no differential effect on the relatively high level of GU toxicity (five-year: 3D-CRT 15.8% vs. IMRT 16.8%) [682]. After a median salvage IMRT dose of 76 Gy, the five-year risk of Grade 2-3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [683].

6.9.5.1.2 Comparison of adjuvant radiotherapy (ART) and salvage radiotherapy

The largest retrospective case-matching study to evaluate ART vs. early SRT included pT3N0 R0/R1 patients only (HT was excluded), 390 out of 500 observation-plus-early-SRT patients (median pre-SRT PSA was 0.2 ng/mL) were propensity matched with 390 ART patients. Two and five years after surgery, biochemically no evidence of disease (bNED) rates were 91% and 78% for ART vs. 93% and 82% after salvage RT, respectively. Subgroup analyses did not yield significant differences for the two approaches. It was concluded that early SRT does not impair PCa control, but clearly helps to reduce over-treatment which is a major issue in ART [684]. Both approaches (ART and SRT) together with the efficacy of neoadjuvant HT are currently being compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d'Etude des Tumeurs Uro-Génitales (GETUG 17).

Decision-making on whether to proceed with adjuvant RT for high-risk PCa - pT3-4 pN0 M0 with undetectable PSA after RP, or to postpone RT as an early salvage procedure in the case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before RP that adjuvant RT may be administered if the patient has negative prognostic risk factors.

6.9.5.2 Hormonal therapy

Currently there is only one underpowered still unpublished RCT comparing the effect of salvage ADT, although retrospective comparative studies are available. The EAU Guidelines Panel conducted a SR including studies published from 2000 onwards [685]. The key findings are summarised below:

Conflicting results on the clinical effectiveness of HT after previous curative therapy of the primary tumour were found. Some studies reported a favourable effect of HT, including the only RCT addressing the research question of this review (86% vs. 79% advantage in OS in the early HT group) [686]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [687]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic work-up and follow-up in these patients.

The studied population is highly heterogeneous regarding their tumour biology and therefore clinical course. The following factors were found predictive for poor outcomes (CRPC, distant metastases [DM], CSS, OS): short PSA-DT, high Gleason score, high PSA, increased age and comorbidities. In some studies, such as the Boorjian, *et al.* study [622], high-risk patients, mainly defined by a high Gleason score and a short PSA-DT (most often < 6 months), seem to benefit most from (early) HT, especially in men with a long life expectancy.

No data were found on the effectiveness of different types of HT, although it is unlikely that this will have a significant impact on survival outcomes in this setting. Non-steroidal anti-androgens have been claimed to be inferior compared to castration, but this difference was not seen in M0 patients [628]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [688]. A small advantage was found in some QoL domains but not overall QoL outcomes. An important limitation of this RCT is the lack of any stratifying criteria such as PSA-DT or initial risk factors.

Based on the lack of definitive efficacy and the undoubtedly associated significant side effects, not all patients with recurrence after primary curative therapy should receive standard HT. Only a minority of them will progress to metastases or PCa-caused death. The objective of HT should be to improve OS, postpone DM, and improve QoL. Biochemical response to only HT holds no clinical benefit for a patient. For older patients and those with comorbidities, the side effects of HT may even decrease life expectancy; in particular, cardiovascular risk factors need to be considered [689, 690]. Early HT should be reserved for those at highest risk of disease progression, defined mainly by a short PSA-DT at relapse (< 6-12 months) or a high initial Gleason score (> 7), and a long life expectancy. In all other situations, the potential benefits of salvage HT should be judiciously considered and balanced against its potential harms.

6.9.5.3 Observation

Observation until the development of clinically evident metastatic disease may represent a viable option for patients with low-risk features (PSA-DT > 12 months, time to BCR > 3 years, GS ≤ 7 and stage ≤ T3a) or unfit patients with a life expectancy < 10 years and/or are unwilling to undergo salvage treatment. In unselected relapsing patients, the median actuarial time to the development of metastasis will be eight years and the median time from metastasis to death will be a further five years [378].

6.9.6 Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or local procedures such as SRP, cryotherapy, interstitial brachytherapy and HIFU [691-700]. Strong recommendations regarding the choice of any of these techniques cannot be made as the available evidence for these treatment options is of (very) low quality. The following is an overview of the most important findings regarding each of these techniques with a proposal for their indications.

6.9.6.1 Salvage radical prostatectomy

Salvage RP (SRP) after RT has the longest history and best likelihood of local control relative to other salvage treatments. However, this must be weighed against the possible adverse events, which are increased compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation.

6.9.6.1.1 Oncological outcomes

In a recent SR of the literature, Chade, *et al.* showed that SRP gave five- and ten-year BCR-free survival (BCR-FS) estimates ranging from 47-82% and from 28-53%, respectively. The ten-year CSS and OS rates ranged from 70-83% and from 54-89%, respectively. The pre-SRP PSA value and prostate biopsy Gleason score were the strongest predictors of the presence of organ-confined disease, progression, and CSS [701].

In most contemporary series, organ-confined disease, negative surgical margins (SM), and the absence of seminal vesicle and/or LN metastases were favourable prognostic indicators associated with a better DFS of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [700].

Table 6.9.2: Oncological results of selected salvage radical prostatectomy case series, including at least 30 patients

Reference	n	Median FU (mo)	Pathologic organ-confined (%)	PSM (%)	Lymph-node involvement (%)	BCR-free probability (%)	CSS (%)	Time probability (yr)
Sanderson, <i>et al.</i> 2006 [702]	51	-	25	36	28	47	-	5
Leonardo, <i>et al.</i> 2009 [703]	32	35	53	34	0	75	-	3
Heidenreich, <i>et al.</i> 2010 [699]	55	23 (2-56)	73	11	20	87	-	2
Chade, <i>et al.</i> 2011 [704]	404	55	55	25	16	37	83	10

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; PSM = positive surgical margin; CSS = cancer-specific survival.

6.9.6.1.2 Morbidity

Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs 3.5%), urinary fistula (4.1% vs 0.06%), abscess (3.2% vs 0.7%) and rectal injury (9.2 vs. 0.6%) [705]. In more recent series, these complications appear to be less common [698, 701]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [701].

Table 6.9.3: Perioperative morbidity in selected salvage radical prostatectomy case series, including at least 30 patients

Reference	n	Rectal injury (%)	Anastomotic stricture (%)	Clavien 3-5 (%)	Blood loss, mL, mean, range
Stephenson, <i>et al.</i> 2004 [698]	100	15 vs. 2*	30	33 vs. 13*	-
Ward, <i>et al.</i> 2005 [706]	138	5	22	-	-
Sanderson, <i>et al.</i> 2006 [702]	51	2	41	6	-
Gotto, <i>et al.</i> 2010 [705]	98	9	41	25	-
Heidenreich, <i>et al.</i> 2010 [699]	55	2	11	3.6	360 (150-1450)

* SRP performed before vs. after 1993.

n = number of patients.

6.9.6.2 Summary of salvage radical prostatectomy

In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least ten years, a pre-SRP PSA < 10 ng/mL and biopsy Gleason score ≤ 7, no LN involvement or evidence of distant metastatic disease pre-SRP, and who's initial clinical staging was T1 or T2 [701]. A meta-regression analysis suggested that SRP may be associated with worse continence outcomes than non-surgical approaches [707].

6.9.7 Salvage cryoablation of the prostate

6.9.7.1 Oncological outcomes

In cases in which RT fails, salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to SRP, as it has a potentially lower risk of morbidity and equal efficacy. However, the very few studies available have shown disappointing results. In a review of the use of SCAP for recurrent cancer after RT, the five-year BDFS estimates ranged from 50-70%. A durable response can be achieved in ~50% of patients with a pre-SCAP PSA < 10 ng/mL [708]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the five-year BCR-free survival (BCR-FS) estimate according to the Phoenix criteria was 54.5 ± 4.9%. Positive biopsies were observed in 15/46 patients (32.6%) who underwent prostate biopsy after SCAP [709].

A case-matched control study comparing SRP and SCAP was performed in men with recurrent PCA after RT. The authors compared the oncological outcomes of the two salvage treatment options after mean follow-up periods of 7.8 (SRP group) and 5.5 years (SCAP group). The five-year BCR-FS was 61% following SRP, significantly better than the 21% detected after SCAP. The five-year OS was also significantly higher in the SRP group (95% vs. 85%) [710].

Table 6.9.4: Oncological results of selected salvage cryoablation of the prostate case series, including at least 50 patients

Reference	n	Median FU (mo)	BCR-free probability (%)	Time probability (yr)	Definition of failure
Pisters, <i>et al.</i> 1997 [710]	150	17	44	-	Nadir + 0.2
Bahn, <i>et al.</i> 2003 [711]	59	82	59	7	PSA > 0.5
Ismail, <i>et al.</i> 2007 [708]	100	33	73 (low risk)	5	ASTRO
Pisters, <i>et al.</i> 2008 [709]	279	22	58	5	ASTRO and Phoenix
Williams, <i>et al.</i> 2011 [712]	187	7.46 yr	39	10	Nadir +2
Spies, <i>et al.</i> 2010 [713]	450	40.8	34	-	PSA > 0.5

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients.

6.9.7.2 Morbidity

According to Cespedes, *et al.* [714], the risks of urinary incontinence and ED at least twelve months after SCAP were as high as 28% and 90%, respectively. In addition, 8-40% of patients reported persistent rectal pain, and an additional 4% of patients underwent surgical procedures for the management of treatment-associated complications. In a recent study by Pisters, *et al.*, the urinary incontinence rate was 4.4%. The rectal fistulae rate was 1.2% and 3.2% of patients required a TURP for removal of sloughed tissue [709]. With the use of third-generation technology, complications such as urinary incontinence and obstruction/retention have significantly decreased during the last decade (see Table 6.9.5) [715].

Table 6.9.5: Perioperative morbidity, erectile function and urinary incontinence in selected salvage cryoablation of the prostate case series, including at least 50 patients

Reference	n	Incontinence (%)	Obstruction/Retention (%)	Rectourethral fistula (%)	ED (%)
Pisters, <i>et al.</i> 1997 [716]	150	73	67	1	72
Bahn, <i>et al.</i> 2003 [711]	59	8	-	3.4	-
Ismail, <i>et al.</i> 2007 [708]	100	13	4	1	-
Pisters, <i>et al.</i> 2008 [709]	279	4.4	3.2	1.2	-
Ahmad, <i>et al.</i> 2013 [717]	283	12	7	1.8	83

ED = erectile dysfunction; n = number of patients.

6.9.7.3 Summary of salvage cryoablation of the prostate

In general, SCAP should be considered only for patients with low comorbidity, a life expectancy of at least ten years, an initial organ-confined PCa cT1c to cT2, initial Gleason score ≤ 7 , a pre-salvage PSA-DT ≥ 16 months and a pre-salvage PSA < 10 ng/mL.

6.9.8 Salvage brachytherapy for radiotherapy failure

Although there is no role for salvage EBRT following local recurrence after previous definitive RT, for carefully selected patients with primary localised PCa and histologically proven local recurrence, HDR- or LDR brachytherapy remain effective treatment options with an acceptable toxicity profile [718-720]. However, the published series are relatively small and consequently this treatment should be offered in experienced centres only. Fifty-two patients were treated at the Scripps Clinic with HDR-brachytherapy over a period of nine years [718]. With a median follow-up of 60 months the five-year biochemical control was 51% and only 2% Grade 3 GU toxicities were reported. Comparable with these data, 42 patients were treated in a phase-II-trial at MSKCC in New York [721]. Of note, the median pre-treatment dose was 81 Gy given with IMRT and the prescription HDR-dose of 32 Gy was delivered in four fractions over 30 hours. The biochemical relapse-free survival after five years was 69% (median follow-up 36 months). Grade 2 late side effects were seen in 15% and one patient developed Grade 3 incontinence. However, older data with higher rates of side effects have been reported [722].

Using LDR-brachytherapy with 103 palladium (Pd), long-term outcome was reported in 37 patients with a median follow-up of 86 months [719]. The biochemical control rate after ten years was 54%. However, the crude rate of \geq Grade 2 toxicity was 46% and \geq Grade 3 toxicity was 11%. These side effects were comparable with a series of 31 patients treated with salvage I-125 brachytherapy in the Netherlands. Therefore, in these small series, late side effects seem to be lower with HDR-brachytherapy [723]. In conclusion, freedom from BCR after salvage HDR and LDR-brachytherapy is promising and the rate of severe side effects in experienced centres seem to be acceptable. Salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

6.9.9 Salvage high-intensity focused ultrasound

6.9.9.1 Oncological outcomes

Salvage HIFU has more recently emerged as an alternative thermal ablation option for radiation-recurrent PCa. Most of the data were generated by one high-volume centre. Median follow-up was very short, and outcome measures were non-standardised.

Table 6.9.6: Oncological results of selected salvage high-intensity focused ultrasound case series, including at least 20 patients

Reference	n	Median FU (mo)	BCR-free probability (%)	Negative biopsy rate
Colombel, <i>et al.</i> 2006 [724]	224	15-18	-	80
Gelet, <i>et al.</i> 2000 [725]	-	-	-	-
Gelet, <i>et al.</i> 2004 [726]	-	-	-	-
Uchida, <i>et al.</i> 2011 [727]	22	24	59 (Phoenix) (24 mo.)	92 (only 12 biopsied)
Berge, <i>et al.</i> 2011 [728]	46	9	60.9 (9 mo)	-

FU = follow-up; mo = months; n = number of patients.

6.9.9.2 Morbidity

Again, most of the data were generated by one high-volume HIFU centre. Important complication rates were mentioned and are at least comparable to other salvage treatment options.

6.9.9.3 Summary of salvage high-intensity focused ultrasound

There is a lack of data which prohibits any recommendation regarding the indications for salvage HIFU.

6.9.10 Observation

Patients who have signs of only local recurrence (i.e., low-risk patients with late recurrence and a slow PSA rise) who do not wish to undergo second-line curative options are best managed by observation alone. A retrospective cohort analysis of HT vs. WW in 248 men with PSA failure after RT showed no advantage for HT in the subgroup of men with a PSA-DT of > 12 months after RT. The five-year metastasis-free survival rate was 88% with HT vs. 92% with WW ($p = 0.74$) [729].

6.9.11 Salvage lymph node dissection

Novel imaging modalities improve the early detection of nodal metastases [730]. The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [730-732]. The majority of treated patients showed biochemical recurrence but clinical recurrence-free and cancer specific ten-year survival over 70% has been reported [731, 733]. Neither the template nor the real value of nodal salvage dissection is available. It must however be remembered that the imaging modalities under-evaluate the real nodal involvement. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [576]. Addition of RT to the lymphatic template after salvage LND may improve the BCR rate [734]. The real efficacy of this salvage procedure remains unproven, as is its impact on survival [735].

6.9.11.1 Guidelines for salvage lymph node dissection

Recommendation	GR
Discuss salvage lymph node dissection (LND) with men experiencing nodal recurrence after local treatment but it should be considered experimental and biochemical recurrence after salvage LND occurs in the majority of cases.	C

6.9.12 Guidelines for second-line therapy after treatment with curative intent

Local salvage treatment	LE	GR
Recommendations for biochemical recurrence after radical prostatectomy		
Offer patients with a prostate-specific antigen (PSA) rise from the undetectable range and favourable prognostic factors ($\leq pT3a$, time to biochemical recurrence > 3 year, PSA-doubling time [DT] > 12 months, Gleason score ≤ 7), active surveillance and possibly delayed salvage radiotherapy.	3	B
Treat patients with a PSA rise from the undetectable range with salvage radiotherapy (SRT). The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	2	A
Recommendations for biochemical recurrence after radiotherapy		
Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy (SRP).	3	B
Due to the increased rate of side effects, perform SRP in experienced centres.	3	A
Offer/discuss high intensity focused ultrasound, cryosurgical ablation and salvage brachytherapy to/with patients without evidence of metastasis and with histologically proven local recurrence. Inform patients about the experimental nature of these approaches.	3	B
Recommendations for systemic salvage treatment		
Do not routinely offer androgen-deprivation therapy (ADT) to asymptomatic men with biochemical recurrence.	3	A
Do not offer ADT to patients with a PSA-DT > 12 months.	3	B
If salvage ADT (post-primary radiotherapy) is started, offer intermittent therapy to responding patients.	1b	A

6.10 Treatment: Castration-resistant PCa (CRPC)

Table 6.10.1: Definition of Castration-resistant PCa (CRPC)

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;	
a)	Biochemical progression: Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or,
b)	Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [736]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

6.10.1 Non-metastatic castration-resistant PCa

Frequent post-treatment PSA surveillance has resulted in earlier detection of progression. Although approximately one-third of men with a rising PSA will develop bone metastases within two years [737], there are no available studies suggesting a benefit for immediate treatment.

In men with CRPC and no detectable clinical metastases, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis-free and OS [737, 738]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group [739] suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative it should be repeated when the PSA reached 5 ng/mL and again after every doubling of the PSA based on PSA-testing every three months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level.

6.10.2 Metastatic castration-resistant PCa

The remainder of this Section focuses on the management of men with proven metastatic CRPC (mCRPC).

6.10.2.1 Conventional androgen deprivation in castration-resistant PCa

Eventually men with PCa show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [740, 741]. However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression and therefore it should be continued indefinitely in these patients.

Table 6.10.2: Randomised phase III controlled trials - first-line treatment of metastatic castration-resistant PCa*

Author	Intervention	Comparison	Selection Criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 2004 [742]	docetaxel/EMP, every 3 weeks, 60 mg/m ² , EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m ² prednisone 5 mg BID		OS: 17.52 vs. 15.6 mo. (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) PFS: 6.3 vs. 3.2 mo. (p < 0.001)
TAX 327 2008 [609, 743]	docetaxel, every 3 weeks, 75 mg/m ² prednisone 5 mg BID Or docetaxel, weekly, 30 mg/m ² prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m ² , Prednisone 5 mg BID		OS: 19.2 for 3 weekly vs. 17.8 mo. for weekly and 16.3 in the control group. (p = 0.004, HR: 0.79 95% CI: 0.67-0.93)

ABIRATERONE				
COU-AA-302 Ryan, <i>et al.</i> 2013 [744-746]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	OS: 34.7 vs. 30.3 mo. (HR: 0.81 p = 0.0033). FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo. p < 0.0001)
ENZALUTAMIDE				
PREVAIL Beer, <i>et al.</i> 2014 [747]	enzalutamide	placebo	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - 10% had visceral mets.	OS: 32.4 vs. 30.2 mo. (p < .001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84) rPFS: 20.0 mo. vs. 5.4 mo. HR: 0.186 (95% CI: 0.15-0.23) p < 0.0001)
SIPULEUCEL-T				
Kantoff, <i>et al.</i> 2010 [748]	sipuleucel-T [615]	placebo [615]	- Some with previous docetaxel. - ECOG 0-1. - Asymptomatic or minimally symptomatic.	OS: 25.8 vs. 21.7 mo. (p = 0.03 HR: 0.78, 95% CI: 0.61-0.98). FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo. (no difference)
Small, <i>et al.</i> 2006 [749]	sipuleucel-T [749]	Placebo [96]	- ECOG 0-1. - No visceral metastases. - No bone or cancer pain. - No corticosteroids.	OS: 25.9 vs. 21.4 mo (p. 01). FU: 36 mo. PFS: 11.7 vs. 10.0 wk.

BID = twice a day; *ECOG* = Eastern Cooperative Oncology Group; *EMP* = estramustine; *FU* = follow-up; *PFS* = progression-free survival; *rPFS* = radiographic progression free survival; *OS* = overall survival.

6.10.3 First-line treatment of metastatic castration-resistant PCa

6.10.3.1 Abiraterone

Abiraterone was evaluated in 1,088 chemo-naïve mCRPC patients in the phase III trial COU-AA-302. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [744]. The main stratification factors were Eastern Cooperative Oncology Group (ECOG) PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and radiographic PFS (rPFS) were the co-primary endpoints. After a median follow-up of 22.2 months, there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, p < 0.001) and the trial was unblinded. At the final analysis with a median follow-up of 49.2 months the OS endpoint was significantly positive (34.7 vs. 30.3 months, HR: 0.81, 95% CI: 0.70-0.93, p = 0.0033) [746]. Adverse events (AEs) related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly Grade 1-2. Sub-set analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [750].

6.10.3.2 Enzalutamide

A randomised phase III trial (PREVAIL) [747] included a similar patient population and compared enzalutamide and placebo. Men with visceral metastases were accepted although the numbers were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naïve mCRPC population of 1,717 men and showed a significant improvement in both co-primary endpoints, rPFS (HR: 0.186; CI: 0.15-0.23, p < 0.0001), and OS (HR: 0.706; CI: 0.6-0.84, p < 0.001). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension and again it was equally well tolerated in men > 75 years [751] as well as in those with or without visceral metastases [752]. For the subgroup of visceral metastases, there seems to be limited benefit concerning OS [752]. Enzalutamide has also been compared with bicalutamide in a phase II study [753] revealing a significant improvement in PFS (15.7 months vs. 5.8 months, HR 0.44, p < 0.0001).

6.10.3.3 Docetaxel regimen

A significant improvement in median survival of 2-2.9 months occurred with docetaxel-based chemotherapy

compared to mitoxantrone + prednisone therapy [742, 743]. The standard first-line chemotherapy is docetaxel 75 mg/m² three-weekly doses combined with prednisone 5 mg BID, up to ten cycles. Prednisone can be omitted if there are contraindications or no major symptoms.

Several poor prognostic factors have been described before docetaxel treatment: PSA > 114 ng/mL, PSA-DT < 55 days, or the presence of visceral metastases [754]. A better risk group definition was subsequently presented, again based on the TAX 327 study cohort: the independent prognostic factors were visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine. Patients were categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), showing three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [755].

Age by itself is not a contraindication to docetaxel [610] but attention must be paid to closer monitoring and comorbidities as discussed in Section 6.7.2.2.2 [756]. In men with mCRPC who are thought to be unable to tolerate the standard regime the data shows that docetaxel 50 mg/m² every two weeks seems well tolerated with less Grade 3-4 AEs and suggest a prolonged time to treatment failure [757].

6.10.3.4 Sipuleucel-T

In 2010, a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [738]. After a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, leading to a significant HR of 0.78 (p = 0.03). No PSA decline was observed and PFS was equivalent in both arms. The overall tolerance was very good, with more cytokine-related AEs Grade 1-2 in the sipuleucel-T group, but the same Grade 3-4 AEs in both arms. In Europe, sipuleucel-T is not available.

Table 6.10.3: Randomised controlled phase III - second-line trials in metastatic castration-resistant PCa*

Author	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
Fizazi, <i>et al.</i> 2012 [614]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	OS: 15.8 vs. 11.2 mo (p < 0.0001). FU: 20.2 mo.
de Bono, <i>et al.</i> 2011 [611]				Radiologic PFS: no change OS: 14.8 vs. 10.9 mo. (p < 0.001 HR: 0.65; 95% CI: 0.54-0.77). FU: 12.8 mo. Radiologic PFS: 5.6 vs. 3.6 mo.
Radium-223				
Parker, <i>et al.</i> 2013 [758]	radium-223	Placebo	Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.	OS: 14.9 vs. 11.3 mo. (p = 0.002, HR: 0.61; 95% CI: 0.46-0.81). All secondary endpoints show a benefit over best standard of care
CABAZITAXEL				
Bahl, <i>et al.</i> 2013 [617]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel. ECOG 0-2.	OS: 318/378 vs. 346/377 events (odds ratio 2.11; 95% CI: 1.33-3.33). FU: 25.5 months OS ≥ 2y 27% vs. 16% PFS: -
deBono, <i>et al.</i> 2010 [613]				OS: 15.1 vs. 12.7 mo. (p < 0.0001, HR: 0.70; 95% CI: 0.59-0.83). FU: 12.8 mo. PFS: 2.8 vs. 1.4 mo. (p < 0.0001, HR: 0.74; 95% CI: 0.64-0.86)

ENZALUTAMIDE				
Scher, <i>et al.</i> 2012 [612]	enzalutamide	Placebo	Previous docetaxel. ECOG 0-2.	OS: 18.4 vs. 13.6 mo. ($p < 0.001$) HR: 0.63; 95% CI: 0.53-0.75). FU: 14.4 mo. Radiologic PFS: 8.3 vs. 2.9 mo. HR: 0.40; 95% CI: 0.35-0.47 $p < 0.0001$)

*Only studies reporting survival outcomes as primary endpoints have been included.

OS = overall survival; PFS = progression-free survival.

6.10.4 Second-line treatment for mCRPC

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.10.3.

6.10.4.1 Cabazitaxel

Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC trial) comparing cabazitaxel + prednisone vs. mitoxantrone + prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [613]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m²) or mitoxantrone (12 mg/m²) + prednisone (10 mg/day), respectively. Overall survival was the primary end-point, which was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months $p < 0.0001$). There was also a significant improvement in PFS (median: 2.8 vs. 1.4 months, $p < 0.0001$), objective RECIST response (14.4% vs. 4.4%, $p < 0.005$), and PSA response rate (39.2% vs. 17.8%, $p < 0.0002$). Treatment-associated WHO Grade 3-4 AEs developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, $p < 0.0002$) but also non-haematological (57.4 vs. 39.8%, $p < 0.0002$) toxicity [759]. In two post marketing randomised phase 3 trials, firstly, cabazitaxel was shown not to be superior to docetaxel in the first line setting and, secondly, it was seen that in the second line setting, 20 mg/m² cabazitaxel is not inferior to 25 mg/m² in terms of OS, but less toxic. Therefore, the lower dose should be preferred [760, 761]. In any case, cabazitaxel should be administered by physicians with expertise in handling neutropenia and sepsis, preferably with prophylactic granulocyte colony-stimulating factor at least in the high-risk patient population [762].

6.10.4.2 Abiraterone acetate after prior docetaxel

Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months [611] and the final results have been reported more recently [614]. A total of 1,195 patients with mCRPC were randomised 2:1 to abiraterone acetate + prednisone or placebo + prednisone. All patients had progressive disease based on the PCWG2 criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary end-point was OS, with a planned HR of 0.8 in favour of abiraterone. After a median follow-up of 20.2 months, the median survival in the abiraterone group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, $p < 0.0001$). The benefit was observed in all subgroups and all the secondary objectives were in favour of abiraterone (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common Grade 3-4 AEs did not differ significantly between the arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly Grade 1-2 (fluid retention, oedema and hypokalaemia).

6.10.4.3 Enzalutamide after docetaxel

The planned preliminary analysis of the AFFIRM study was published in 2012 [612]. This trial randomised 1,199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were received by 30% of the population. The primary end-point was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, $p < 0.001$). This led to the recommendation that the study be halted and unblinded. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side effects was observed in the two groups, with a lower incidence of Grade 3-4 AEs in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

6.10.4.4 Radium-223

The only bone-specific drug that is associated with a survival benefit is radium-223, an α -emitter. In a large

phase III trial (ALSYMPCA), 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo, plus standard of care. The primary end-point was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70; $p < 0.001$) [758]. It was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, this did not differ significantly from that in the placebo arm [758]. Radium-223 was effective and safe no matter if the patients were docetaxel pre-treated, or not [763].

6.10.5 **Treatment after docetaxel and one line of hormonal treatment for mCRPC**

The choice of further treatment after docetaxel and one line of hormonal treatment for mCRPC is open. Either further HT (enzalutamide or abiraterone) or second-line chemotherapy (cabazitaxel) are reasonable options albeit with low levels of evidence. PARP inhibitors have shown high rates of response in men with somatic homologous recombination deficiency (HRD) in initial studies. Men previously treated with both docetaxel and at least one novel hormonal agent and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate [764]. Patients without HRD did not clearly benefit from olaparib. Although not yet available they offer an exciting opportunity to tailor therapy based on the mutation profile contained within a tumour.

In general however, and in unselected patients, subsequent treatments can be expected to have a smaller response [765, 766] with evidence of cross-resistance between enzalutamide and abiraterone [767].

6.10.6 **Monitoring of treatment**

Baseline examinations should include history and clinical examination as well as baseline bloods (PSA, FBC, renal function, LFTs, ALP), bone scan and CT of chest abdomen and pelvis [768]. Prostate-specific antigen alone is not reliable enough [769] for monitoring disease activity in advanced CRPC, since visceral metastases may develop in men without rising PSA [770]. Instead PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [742]. A majority of experts at a recent consensus meeting suggested regular review and repeat blood profile every two to three months with bone scintigraphy and CT scans at least every six months, even in the absence of a clinical indication [768]. This reflects that the agents with a proven OS survival benefit all have potential toxicity and considerable cost and patients with no objective benefit should have treatment modified. This panel stressed that such treatments should not be stopped for PSA progression alone. Instead at least two of three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment. For trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions and introduced the concept of “no longer clinically benefiting” to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [771]. These recommendations also seem valid for clinical practice outside trials.

6.10.7 **When to change treatments**

The timing of mCRPC treatment change remains a matter of debate in mCRPC although it is clearly advisable to start or change treatment immediately in men with symptomatic progressing metastatic disease. As the number of effective treatments increases and without head to head trials or data assessing the effectiveness of different sequencing options, it is not clear how to choose the appropriate “second-line” treatment. In the absence of other data, the inclusion criteria from licensing trials have been used to prioritise treatment sequencing.

The Eastern Cooperative Oncology group PS have been used to stratify patients. Generally men with a PS of 0-1 are likely to tolerate treatments and those with PS of 2 or more are less likely to benefit. However, it is important that treatment decisions are individualised. This applies particularly where symptoms related to disease progression are determining PS. In such cases it may be appropriate to trial novel treatments to establish if treatment would improve PS. A summary of the issues regarding sequencing are discussed in a paper published following the St. Gallen Consensus Conference [768].

6.10.8 **Symptomatic management in metastatic castration-resistant PCa**

Castration-resistant PCa is usually a debilitating disease, often affecting the elderly male. A multidisciplinary approach is often required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers [772]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression, which often occur.

6.10.8.1 **Common complications due to bone metastases**

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective [773],

even as a single fraction [774]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [775]. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture, whatever its origin, clearly improving both pain and QoL [776]. However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [777, 778]. Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery consultation should be planned to discuss a possible decompression, followed by EBRT [779]. Otherwise, EBRT, with or without systemic therapy, is the treatment of choice.

6.10.9 Preventing skeletal-related events

6.10.9.1 Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anticancer treatments but docetaxel were available. 643 patients who had CRPC [780] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every three weeks for fifteen consecutive months, or placebo. The 8 mg dose was poorly tolerated and reduced to 4 mg but did not show a significant benefit. However, at fifteen and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer skeletal-related events (SREs) compared to the placebo group (44 vs. 33%, $p = 0.021$) and in particular fewer pathological fractures (13.1 vs. 22.1%, $p = 0.015$). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.10.9.2 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κ B ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85, $p = 0.028$) [779]. This benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively) and neither the FDA nor the EMA have approved denosumab for this indication [781].

The efficacy and safety of denosumab ($n = 950$) compared with zoledronic acid ($n = 951$) in patients with metastatic CRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs, as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR: 0.82; $p = 0.008$). Both urinary N-telopeptide (NTX) and bone-specific alkaline phosphatase (BAP) were significantly suppressed in the denosumab arm compared with the zoledronic acid arm ($p < 0.0001$ for both). However, these findings were not associated with any survival benefit and in a recent *post-hoc* re-evaluation of endpoints, denosumab showed identical results when comparing skeletal-related events and symptomatic skeletal events [782].

The potential toxicity (e.g., osteonecrosis of the jaw) of these drugs, must always be kept in mind [773, 779]. Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection [783].

6.10.10 Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant PCa

Summary of evidence	LE
No definitive strategy regarding first treatment choice (which drug/drug family first) can be devised.	4
No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy, chemotherapy or radium-223) as no clear predictive factors exist.	3

Recommendations	LE	GR
Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing castration-resistant PCa (CRPC).	4	A
Do not treat patients for non-metastatic CRPC outside of a clinical trial.	3	A
Counsel, manage and treat patients with metastatic (m)CRPC in a multidisciplinary team.	3	A
Treat patients with mCRPC with life prolonging agents. Base the choice of first line treatment on the performance status, symptoms, comorbidities, location and extent of disease (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).	1b	A

6.10.11 **Guidelines for cytotoxic treatment in castrate-resistant PCa**

Recommendations	LE	GR
Counsel, manage and treat patients with metastatic castration-resistant PCa (mCRPC) in a multidisciplinary team.	3	A
Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m ² every three weeks.	1a	A
In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include cabazitaxel, abiraterone, enzalutamide and radium-223.	1a	A
Base second-line treatment decisions of mCRPC on pre-treatment performance status, comorbidities and extent of disease.		B

6.10.12 **Guidelines for supportive care of castrate-resistant PCa**

These recommendations are in addition to appropriate systemic therapy.

Recommendations	LE	GR
Offer bone protective agents to patients with metastatic castration-resistant PCa (mCRPC) and skeletal metastases to prevent osseous complications.	1a	B
Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	1b	A
Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, and adequate use of analgesics.	1a	B
In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	1b	A

7. FOLLOW-UP

7.1 Follow-up: After local treatment

7.1.1 Definition

Local treatment is defined as RP or RT, either by EBRT or low- or high-dose brachytherapy, or any combination of these. Unestablished alternative treatments, such as HIFU and cryosurgery do not have a well-defined, validated PSA cut-off to define BCF, but do follow the general principles as presented in this section.

7.1.2 Why follow-up?

Recurrence occurs after primary therapy in many patients who have previously received treatment with intent to cure. Reasons for follow-up vary depending on treatment, patient age, comorbidity and the patient's own wishes. Patients who receive curative therapy are followed up to:

- assess immediate- and long-term oncological results, side effects or complications of therapy, functional outcomes and to provide psychological support to PCa survivors;
- discuss the possibility of second-line treatment with curative intent; early HT or WW with the patient.

7.1.3 How to follow-up?

The procedures indicated at follow-up visits vary according to clinical situation. The examinations discussed below are routinely used to detect PCa progression or residual disease. Prostate specific antigen level and DRE are the only tests that should be performed routinely. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications must be individualised, which is beyond the scope of these Guidelines. The examinations used most often for cancer-related follow-up after curative surgery or RT are discussed below.

7.1.3.1 Prostate-specific antigen monitoring

Measurement of PSA is a cornerstone in follow-up after local treatment. Expectations differ after RP and RT, but PSA recurrence often precedes clinical recurrence [784, 785]. A single, elevated, serum PSA level should

be confirmed before starting second-line therapy based solely on PSA elevation.

7.1.3.2 *Definition of prostate-specific antigen progression*

The PSA level for definition of treatment failure differs between RP and RT. International consensus defines recurrent cancer after RP by two consecutive PSA rises ≥ 0.2 ng/mL [786]. However, others have argued for a higher cut-off of 0.4 ng/mL for patients at high risk of clinical progression [785].

Ultrasensitive PSA assay remains controversial for routine follow-up after RP. Men with a ultrasensitive PSA nadir < 0.01 ng/mL have a 4% likelihood of early biochemical relapse [787]. Detectable post-operative ultrasensitive PSA does not predict BCR in all cases, although it adds prognostic value. In men with ultrasensitive PSA > 0.05 ng/mL, 66.8% remained free of biochemical disease at five years [788]. If survival is improved by early adjuvant treatment after RP (before PSA reaches > 0.2 ng/mL), higher PSA nadir levels may help identify suitable candidates.

At the 2006 RTOG-ASTRO Consensus conference, a new definition of radiation failure was proposed to establish better correlation between definition and clinical outcome, namely, an increase of 2 ng/mL above the post-treatment PSA nadir [621]. It applies to patients with or without HT.

After HIFU or cryotherapy, no endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of BCF after these alternative local treatments.

7.1.3.3 *Prostate-specific antigen monitoring after radical prostatectomy*

Prostate-specific antigen is expected to be undetectable within six weeks after successful RP [789]. Persistently elevated PSA in patients treated with RP is thought to be due to residual cancer, either micro-metastases or residual pelvic disease.

A rapidly increasing PSA level suggests distant metastases, whereas a later, slowly increasing, level most likely suggests local recurrence. Time to PSA recurrence and tumour differentiation are important predictive factors distinguishing local and systemic recurrence [790]. Local treatment failure and distant metastases occur with undetectable PSA levels. This is rare and occurs mostly in patients with undifferentiated tumours [791].

Thus, in patients with favourable pathology ($< pT3$, $pN0$, Gleason score < 8), PSA measurement and disease-specific history could be a single test in follow-up after RP.

7.1.3.4 *PSA monitoring after radiotherapy*

Prostate-specific antigen level falls slowly after RT compared with RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after RT [792], although the optimal value is controversial. The interval before reaching the nadir can be up to 3 years or more. After RT, PSA-DT is correlated with site of recurrence: patients with local recurrence have a doubling time of thirteen months compared to three months for those with distant failure [793].

7.1.3.5 *Digital rectal examination*

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [791]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. Prostate-specific antigen measurement and DRE comprise the most useful combination for first-line examination in follow-up after RT or RP, but PSA measurement may be the only test in cases with favourable pathology ($< pT3$, $pN0$, Gleason < 8) after RP [794].

7.1.3.6 *Transrectal ultrasound, bone scintigraphy, computed tomography, magnetic resonance imaging, and ^{11}C -choline positron emission tomography computed tomography*

Imaging techniques have no place in routine follow-up of localised PCa. They are only justified in patients with BCF or in patients with symptoms for whom the findings affect treatment decisions. (See Section 6.9.4.5 for a more detailed discussion).

7.1.3.6.1 *Transrectal ultrasonography/magnetic resonance imaging guided biopsy.*

Biopsy of the prostate bed and urethrovesical anastomosis or of the remaining prostate after radiotherapy, are only indicated if local recurrence affects treatment decisions.

7.1.4 **When to follow-up?**

Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years. Patients should be followed up more closely during the initial post-treatment period when risk of failure is highest. Prostate-specific antigen measurement, disease-specific history and DRE are recommended at three, six and twelve months post-operatively, every six months thereafter until three years, and then annually.

The first post-treatment clinic visit mainly focusses on detecting treatment-related complications

and assist patients in coping with their new situation. Tumour or patient characteristics may allow alterations to this schedule. Patients with poorly differentiated and locally advanced tumours or with positive margins may be followed-up more closely than those with a well-differentiated, intracapsular or specimen-confined tumour. Advanced age or associated comorbidity may make further follow-up in asymptomatic patients superfluous.

7.1.5 **Summary of evidence and guidelines for follow-up after treatment with curative intent**

Summary of evidence	LE
After radical prostatectomy serum prostate-specific antigen (PSA) level > 0.2 ng/mL is associated with residual or recurrent disease.	2a
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is the most reliable sign of recurrence.	2a
Palpable nodules and increasing serum PSA are signs of local recurrence.	2a

Recommendations	GR
Routinely follow-up asymptomatic patients, by obtaining a disease-specific history and serum prostate-specific antigen (PSA) measurement supplemented by digital rectal examination (DRE). These should be performed at three, six and twelve months after treatment, then every six months until three years, and then annually.	B
Imaging to detect local recurrence is only recommended if it affects treatment planning. Biopsy is usually not necessary before second-line therapy.	B
Do not routinely offer bone scans and other imaging modalities to asymptomatic patients if there are no signs of biochemical relapse. In case patients have bone pain or other symptoms of progression, re-staging should be considered irrespective of serum PSA level.	B

7.2 **Follow-up: During hormonal treatment**

7.2.1 **Introduction**

Follow up must be individualised as BCF might be associated with rapid symptomatic progression or evolve without progression on imaging or symptoms over years.

7.2.2 **Purpose of follow-up**

The main objectives of follow-up in these patients are to ensure treatment compliance, to monitor treatment response and side effects, and to guide the treatment at the time of CRPC.

Complementary investigations must be restricted to those that are clinically helpful to avoid unnecessary examinations and costs. Based on current knowledge, it is not possible to formulate level 1 evidence guidelines for follow-up during HT.

7.2.3 **Methods of follow-up**

7.2.3.1 **Clinical follow-up**

Clinical follow-up is mandatory on a regular basis, and cannot be replaced, neither by laboratory test biology nor imaging modalities. Of utmost importance in metastatic situations is to advise patients about early signs of spinal cord compression, check for occult cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk.

7.2.3.1.1 **Prostate-specific antigen monitoring**

Prostate-specific antigen is a key marker for following the course of androgen sensitive PCa. Treatment response may be assessed using the change in serum PSA level as a surrogate endpoint for survival in patients with newly diagnosed metastatic PCa in locally advanced and metastatic PCa [795], as in salvage ADT for relapse following treatments with curative intent [796].

For intermittent ADT Section 6.6.4.3 may be consulted.

A rise in PSA level usually precedes the onset of clinical symptoms by several months. Importantly, taking into account the PSA level alone is insufficient to define progression as clinical progression (usually bone pain) with a stable PSA has been reported.

7.2.3.1.2 **Creatinine, haemoglobin and liver function monitoring**

Creatinine monitoring is good clinical practice as an increase may be linked to bilateral ureteral obstruction or bladder retention. Liver function tests may suggest treatment toxicity (especially NSAA), or rarely disease

progression. A decline in haemoglobin after three months of ADT is independently associated with a shorter progression-free and OS rate [797] and might explain significant fatigue. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis [798]. Therefore, it may be helpful to determine bone-specific isoenzymes as none are directly influenced by HT.

7.2.3.1.3 Bone scan, ultrasound and chest X-ray

Asymptomatic patients with a stable PSA level should not undergo imaging at regular intervals [799]. New symptomatic bone lesions require a bone scan, as well as a PSA progression suggesting CRPC status, if a treatment modification is considered. The Prostate Cancer Clinical Trials Working Group has clarified the definition of bone scan progression as the appearance of at least two new lesions [742], later confirmed.

Suspicion of disease progression indicates the need for additional imaging modalities, guided by symptoms or possible subsequent treatments. In CRPC, imaging must be individualised with the aim of maintaining the patient's QoL.

7.2.3.1.4 Testosterone monitoring

This should be considered part of clinical practice for men on LHRH therapy. Most patients receiving LHRH analogues will achieve castrate serum testosterone levels (< 50 ng/mL). However, approximately 13-38% of patients fail to achieve this goal and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [525], known as the 'acute on-chronic effect' or 'breakthrough response'.

The timing of measurements is not clearly defined. A three to six-month testosterone level assessment is suggested to ensure castration is achieved and maintained. If not, switching to another agonist or antagonist, or to an orchiectomy should be considered. In patients with rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castrate-resistant state.

7.2.3.1.5 Monitoring of metabolic complications

Androgen deprivation therapy has a greater range of complications than might be expected. The most severe are metabolic syndrome, cardiovascular morbidity and bone problems, (see Section 8.2.4.5). The patient's general practitioner should probably be more involved at this stage.

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and regularly), as for blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. A cardiology consultation should be considered in men with a history of cardiovascular disease and men older than 65 years prior to starting ADT. Monitoring serum levels of vitamin D and calcium is important (see Section 6.7.2.2.1). It is suggested that routine bone monitoring should be performed every two years during castration [800], or yearly if there are other risk factors [801, 802]. However, there is no high level evidence that this recommendation improves bone complications due to ADT, and prospective trials are needed.

Patients on ADT should be given advice on modifying their lifestyle (e.g. diet, exercise, smoking cessation, etc.) and should be treated for any existing conditions, such as diabetes, hyperlipidaemia, and/or hypertension [797, 798]. Furthermore, the risk-to-benefit ratio of ADT must be considered in patients with a higher risk of cardiovascular complications, especially if it is possible to delay starting ADT.

7.2.4 **When to follow-up**

After the initiation of ADT, it is recommended that patients are followed at three to six months intervals. This must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms.

7.2.4.1 *Stage M0 - M1 patients*

If there is a good treatment response, i.e. PSA response (< 4 ng/mL), symptomatic improvement, good psychological coping, good treatment compliance, follow-up visits are scheduled every three to six months.

7.2.4.2 *Castration-refractory PCa*

Patients whose disease progresses, or who do not respond according to the criteria mentioned above, warrant an individualised follow-up scheme.

7.2.5 **Guidelines for follow-up during hormonal treatment**

Recommendations	GR
Evaluate patients at three to six months after the initiation of treatment.	A
As a minimum, tests should include serum prostate-specific antigen (PSA) measurement, digital rectal examination (DRE), serum testosterone, and careful evaluation of symptoms in order to assess the treatment response and side effects.	A
In patients undergoing intermittent androgen deprivation, monitor PSA and testosterone at fixed intervals during the treatment pause (monthly or at three-month intervals).	A
Adapt follow-up to the individual patient, according to stage of disease, prior symptoms, prognostic factors and the treatment given.	A
In patients with stage M0 disease with a good treatment response, schedule follow-up every six months. As a minimum requirement, include a disease-specific history, DRE and serum PSA determination in the diagnostic work-up.	A
In patients with stage M1 disease with a good treatment response, schedule follow-up every three to six months. As a minimum requirement, include a disease-specific history, DRE, serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year.	A
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	A
When disease progression occurs, or if the patient does not respond to treatment, adapt/individualise follow up.	A
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa (CRPC) requires a testosterone level < 50 ng/mL (< 1 mL/L).	B
Do not offer routine imaging to otherwise stable patients.	B

8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first will summarise consequences of therapies for PCa. Based on two SRs, the second will evaluate the evidence for adverse effects of treatments over the longer-term (twelve months +) and also make evidence-based recommendations for supportive interventions aimed at improving disease-specific QoL across all stages of disease.

8.1 Introduction

Quality of life and personalised care go hand in hand. Treating prostate cancer can affect an individual both physically and mentally, as well as his close relations and his work or vocation. These multifaceted issues all have a bearing on his perception of 'quality of life' [803]. Approaching care from a holistic point of view requires the intervention of a multi-disciplinary team ranging from urologist, medical oncologist, radiation oncologist, oncology nurse to psychologists and many others. Attention to the psychosocial concerns of men with prostate cancer is integral to quality clinical care, and this includes the needs of carers and partners [762]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL. Taking QoL into consideration relies on understanding the patient's wishes and preferences so that optimal treatment proposals can be formulated and discussed.

8.2 Adverse effects of prostate cancer therapies

8.2.1 Surgery

Post-operative incontinence and ED are common problems following surgery for PCa. A key consideration is whether these problems are reduced by using newer techniques such as RALP. Recent SRs have documented complication rates after RALP [388, 390-393], and can be compared with contemporaneous reports after RRP [398]. From these reports, the mean continence rates at twelve months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP. There is, as yet, no evidence from retrospective studies of differences in urinary incontinence at twelve months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or ED outcomes. The major limitations of the included studies

were the retrospective study design and the use of different assessment tools preventing comparison between techniques and series. Recently, a prospective, controlled, non-randomised trial of patients undergoing RP in fourteen centres using RALP or RRP was published. At twelve months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The adjusted OR was 1.08 (95% CI: 0.87-1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66-0.98) [394]. A recent RCT comparing RALP and RRP, has reported outcomes at twelve weeks in 326 patients [334]. Functional outcomes were similar in the two groups, but longer follow up is needed to report on longer term effects. The intra- and peri-operative complications of retropubic RP and RALP are listed in Table 8.2.1.

Table 8.2.1: Intra- and peri-operative complications of retropubic RP and RALP (Adapted from [388])

Predicted probability of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Bladder neck contracture	1.0	2.1	4.9
Anastomotic leak	1.0	4.4	3.3
Infection	0.8	1.1	4.8
Organ injury	0.4	2.9	0.8
Ileus	1.1	2.4	0.3
Deep-vein thrombosis	0.6	0.2	1.4
Predicted rates of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Clavien I	2.1	4.1	4.2
Clavien II	3.9	7.2	17.5
Clavien IIIa	0.5	2.3	1.8
Clavien IIIb	0.9	3.6	2.5
Clavien IVa	0.6	0.8	2.1
Clavien V	< 0.1	0.2	0.2

RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy.

8.2.1.1 Early complications of extended lymph node dissection

Pelvic eLND increases morbidity in the treatment of PCa. Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common adverse event. Other authors have reported more acceptable complication rates [804]. Similar rates of lymphoceles have been observed in RALP series, however, in one subgroup analysis, lymphoceles were more common with the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [805, 806]. Briganti *et al.* [807] also showed more complications after extended compared to limited LND. 20% of men suffer a complication of some sort after eLND. Thromboembolic events occur in less than 1% of cases.

8.2.2 Radiotherapy

8.2.2.1 Side effects of external beam radiotherapy

Retrospective studies suggest that RT affects erectile function to a lesser degree than surgery of patients [808], and this has been borne out by the recent ProtecT study results (see below). A meta-analysis has shown that the one-year probability rates for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy + EBRT, 0.55 after EBRT, 0.34 after nerve-sparing RP, and 0.25 after standard RP. When studies with more than two years of follow-up were selected (i.e. excluding brachytherapy), the rates became 0.60, 0.52, 0.25, and 0.25, respectively, with a greater spread between the radiation techniques and surgical approaches [809].

Studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT [810, 811]. In a retrospective evaluation of 30,552 and 55,263 men, who had undergone either EBRT or RP, the risk of being diagnosed with rectal cancer increased by 1.7-fold in comparison with the surgery group [810]. Another analysis [811] showed that the relative risk of developing bladder cancer increased by 2.34-fold in comparison with a healthy control population. On the other hand, a re-analysis of SEER data including more than 100,000 patients, demonstrated a risk of about 0.16% (i.e. 160 cases per 100,000 patients) of radiation-induced malignant tumours [812]. The Memorial Sloan-Kettering Cancer Center group have also reported corresponding data on late toxicity from their experience in 1,571 patients with T1-T3 disease treated with either 3D-CRT or IMRT at doses of between 66 Gy and 81 Gy, with a median follow-up of ten years [813]. Both acute gastrointestinal and GU toxicity appeared to be predictive for corresponding late toxicity. The overall rate of NCIC/Common Toxicity Criteria (CTC) Grade 2 or more

gastrointestinal toxicity was 5% with IMRT vs. 13% with 3D-CRT. The incidence of Grade 2 or higher late GU toxicity was 20% in patients treated with 81 Gy vs. 12% in patients treated with lower doses. The overall incidences of Grade 3 toxicity were 1% for gastrointestinal toxicity and 3% for GU toxicity. These data suggest that IMRT can successfully protect against late gastrointestinal toxicity. Interestingly, with dose escalation, GU toxicity may become the predominant type of morbidity [813].

8.2.2.2 Side effects from brachytherapy

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), with post-implantation TURP reported as being required in up to 8.7% of cases, and incontinence (0-19%) [814]. A small RCT has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity [815]. This observation requires further study in a larger number of patients. Chronic urinary morbidity can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Previous TURP for BPH increases the risk of post-implantation incontinence and urinary morbidity. Prevention of morbidity depends on careful patient selection, and expert assessment of IPSS score, backed up by urodynamic studies if needed is key to this.

A small RCT has suggested that using stranded rather than loose seeds is associated with better seed retention and less seed migration, and this should be the standard choice [816].

Table 8.2.2: Acute gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer morbidity scale (adaptations with regard to the original RTOG scale in italics) according to Huang *et al.* [817]*.

	Grade 1	Grade 2	Grade 3	Grade 4
GI	Increased frequency or change in quality of bowel habits not requiring medication. Rectal discomfort not requiring analgesics.	Diarrhoea requiring parasympatholytic drugs. Mucous discharge not necessitating sanitary pads. Rectal or abdominal pain requiring analgesics.	Diarrhoea requiring parenteral support. Severe mucous or blood discharge necessitating sanitary pads. Abdominal distension (flat plate radiograph demonstrates distended bowel loops).	Obstruction, fistula, or perforation GI bleeding requiring transfusion; Abdominal pain or tenesmus requiring tube decompression or bowel diversion.
GU	Frequency of urination or nocturia twice pretreatment habit. Dysuria or urgency not requiring medication.	Frequency of urination is less frequent than every hour (<i>day: 12-16 times; nocturia 5-8 times</i>). Dysuria, urgency, bladder spasm requiring local anaesthetic.	Frequency of urination is more frequent than every hour (<i>day: >16 times; nocturia: > 8 times</i>). Dysuria, bladder spasm, urgency requiring frequent regular narcotic. Gross haematuria <i>complaints requiring permanent or suprapubic catheter.</i>	Haematuria requiring transfusion Obstruction not resulting from Clots. Ulceration Necrosis

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GI = gastrointestinal; GU = genito-urinary.

Table 8.2.3: Late gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) morbidity scale (adaptations with regard to the original RTOG/EORTC scale in italics) according to Huang *et al.* [817]*

	Grade 1	Grade 2	Grade 3	Grade 4
GI*	Mild diarrhoea Mild cramping Bowel movements 2-5 per day Slight rectal discharge or bleeding	Moderate diarrhoea Intermittent, severe cramping. Bowel movements (5 per day). Moderate excessive, rectal discharge. Intermittent, frequent bleeding (3 single laser treatments or transfusion).	Watery diarrhoea Obstruction requiring surgery. Bleeding requiring surgery or 2 laser treatments or transfusions.	Necrosis Perforation Fistula Abdominal pain or tenesmus requiring tube decompression or bowel diversion.
GU	<i>Frequency during day 0.5-1 h Nocturia 2-3/night Slight dysuria or microscopic haematuria requiring no medication Slight epithelial atrophy, minor telangiectasia Bladder capacity > 300 mL</i>	<i>1-2 h Nocturia 4-6/night Moderate dysuria or intermittent (mild, moderate) haematuria requiring medication† Moderate telangiectasia Bladder capacity: 150-300 mL</i>	<i>Frequency during day: 2 h Nocturia 6/night Severe dysuria Frequent (severe) haematuria Severe telangiectasia Bladder capacity: 100-150 mL Benign urethral strictures requiring TURP, dilation, or suprapubic or permanent catheter</i>	<i>Frequency during day: Necrosis Severe haemorrhagic cystitis Bladder capacity > 100 mL</i>

* The difference between grade 1 and grade 2 GI pain, mucosal loss, or bleeding is most easily made when grade 2 is defined as morbidity requiring specific medication: grade 1 = stool softener, diet modification, occasional (< 2/wk) non-narcotic drug, occasional antidiarrhoeal agent (2/wk), occasional use of incontinence pads (1-2 d/wk); grade 2 = regular (>2/wk) use of (non)narcotic drugs for pain, regular (2/wk) antidiarrhoeals, steroid suppositories, one laser.

† With the exception of antibiotics.

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GI = gastrointestinal; GU = genito-urinary; TURP = transurethral resection of the prostate.

8.2.3 Local treatments other than surgery or radiotherapy

8.2.3.1 Cryosurgery

In Ramsay *et al.*'s systematic review and meta-analysis [511], there was evidence that the rate of urinary incontinence at one year was lower for CSAP than for RP, but the size of the difference decreased with longer follow-up. There was no significant difference between CSAP vs. EBRT in terms of urinary incontinence at one year (< 1%), CSAP had a similar ED rate (range 0-40%) to RP at one year. There was insufficient data to compare CSAP vs. EBRT in terms of ED. There was a general trend for CSAP to have fewer procedural complications, apart from urinary retention. The only difference that reached statistical significance was for urethral stricture, which was less frequent after CSAP than after RP. However, the data underlying this comparison are weak and are, of course, not based on a RCT.

8.2.3.2 High-intensity focused ultrasound

In terms of toxicity, there are insufficient data on urinary incontinence, ED or bowel dysfunction to draw any conclusions, although at one year HIFU had lower statistically significant incontinence rates than RP [511]. The safety profile for HIFU was generally good, the commonest reported complications being dysuria (22-30%), acute urinary retention (range 2-24%), urethral sloughing (up to 22%) and UTI (up to 17%). However, HIFU appeared to have a slightly higher incidence of urethral stricture than EBRT which was statistically significant. The quality of the evidence was poor, due to high risks of bias across studies and heterogeneity of outcome definition, measurement and reporting.

The incontinence rates at one year for focal CSAP were very low. Procedural complication rates were generally low, with the commonest complication being acute urinary retention (range 1.2-8.0%).

8.2.4 **Hormonal therapy**

There is a lack of data on the effects of HT on QoL, with only a single, large, prospective, RCT comparing orchiectomy + flutamide or placebo in M1 patients. Combined therapy resulted in a lower QoL in the first six months, with more frequent diarrhoea and worse emotional functioning, compared with castration alone [818]. A small RCT evaluated the HRQoL at one-year follow-up in patients with non-localised PCa, between various ADT regimens, or no treatment. Both sexual and cognitive function significantly declined with ADT, while emotional distress significantly increased in the no treatment patient group [819]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [820]. Another retrospective, non-randomised study suggested that men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than orchiectomised patients. The stage at diagnosis had no effect on health outcomes [821].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at twelve months [822]. A *post-hoc* analysis, including only patients with sexual interest suggested that bicalutamide was associated with better sexual preservation, including maintained sexual interest, feeling sexually attractive [823], preserved libido and erectile function [824].

Intermittent androgen deprivation has been discussed elsewhere (see Section 6.6 - Metastatic PCa - Hormonal therapy).

8.2.4.1 *Sexual function*

Loss of libido and ED are common. The management of acquired ED is mostly non-specific [825].

8.2.4.2 *Hot flushes*

Hot flushes are the most common side-effect of ADT. They appear three months after starting ADT, usually persist long-term and have a significant impact on QoL.

Oestrogen-receptor modulators or low-dose oestrogen therapies, e.g. DES, 0.5-1 mg/day, reduce the frequency and severity of hot flushes. Both treatments carry a risk of cardiovascular complications. Soy phytoestrogens have shown an efficacy in breast cancer patients, but have not been evaluated in men. Progesterone-based treatments have demonstrated efficacy with 80% of patients showing an improvement [826].

Serotonin re-uptake inhibitors (e.g. venlafaxine or sertraline) appear to be effective in men, but less than HT based on a prospective randomised trial comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or CPA, 100 mg daily [827]. After six months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Venlafaxine was clearly inferior compared to the hormonal agents, which showed similar efficacy to each other.

With a placebo effect influencing up to 30% of patients [828], the efficacy of clonidine, veralipride, gabapentine [829] and acupuncture [830] must be compared in prospective RCTs.

8.2.4.3 *Other systemic side-effects of androgen-deprivation therapy*

Androgen-deprivation therapy is associated with significant side effects which may lead to significantly increased morbidity or even mortality.

8.2.4.4 *Non-metastatic bone fractures*

Due to increased bone turnover and decreased BMD in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% relative risk with long-term ADT) [831]. Hip fractures in men are associated with a significant risk of death [832]. A precise evaluation of BMD should be performed by dual emission X-ray absorptiometry (DEXA) before starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk factors) indicates a high risk of subsequent non-metastatic fracture. The WHO FRAX tool (<http://www.shef.ac.uk/FRAX>) should be used to evaluate individual risk. Obesity (increase in body fat mass by up to 10%) and sarcopenia (decrease in lean tissue mass by up to 3%) are common and occur during the first year of ADT [833]. Both changes increase the fracture risk.

8.2.4.4.1 *Lifestyle changes before starting long-term androgen-deprivation therapy*

Patients should be encouraged to adopt lifestyle changes, e.g. increased physical activity, cessation of smoking, decreased alcohol consumption, and to normalise their BMI. Calcium and vitamin D supplements

should be considered if low values are detected (normal values: calcium: 2.2-2.6 nmol/L, vitamin D: 100-160 nmol/L). A daily intake of at least 1,200 mg/day of calcium and 1,000 UI of vitamin D is useful.

8.2.4.4.2 Hormonal treatment modalities

Bicalutamide monotherapy could be a bone-protective treatment [834, 835], but is limited by its suboptimal efficacy (see Section 6.6 - Metastatic PCa - Hormonal Therapy). The intermittent modality might be associated with less bone impact [565].

8.2.4.4.3 Bisphosphonates

Bisphosphonates increase BMD in the hip and spine by up to 7% in 1 year. The optimal regimen for zoledronic acid remains unclear: quarterly [836] or yearly [837] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [838]. A quarterly regimen could be considered for a BMD \leq 2.5 as a yearly injection is unlikely to provide sufficient protection [839].

In contrast to breast cancer, a significant benefit in OS has only been demonstrated in PCa in a *post-hoc* analysis for the oral first-generation clodronate with an absolute 8% OS increase after eight years of follow-up [840]. This benefit has never been observed with more recent bisphosphonates.

Denosumab (a fully human monoclonal antibody against receptor activator of NF- κ B ligand [RANKL])

In M0 patients, denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after two years, using a 60 mg subcutaneous regimen every six months [841]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs. 3.9%, $p = 0.006$). The benefits were similar whatever the age ($<$ or $>$ 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, e.g. jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every four weeks), a delay in bone metastases of 4.2 months has been shown [782] without any impact on OS, but with an increase in side effects. Therefore, this later regimen cannot be recommended.

8.2.4.5 Metabolic effects

Lipid alterations are common and may occur as early as the first 3 months of treatment [833]. ADT also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. Once again, exercise is strongly recommended for its protective effect. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [842], but there is insufficient data to recommend its use in non-diabetic patients.

Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. The definition requires at least three of the following criteria [843]:

- waist circumference $>$ 102 cm;
- serum triglyceride $>$ 1.7 mmol/L;
- blood pressure $>$ 130/80 mmHg or use of medication for hypertension;
- high-density lipoprotein (HDL) cholesterol $<$ 1 mmol/L;
- glycaemia $>$ 5.6 mmol/L or the use of medication for hyperglycaemia.

The prevalence of a metabolic-like syndrome is higher during ADT compared with men not receiving ADT [844].

8.2.4.6 Cardiovascular morbidity

Cardiovascular mortality is now the most common cause of death in PCa patients, even exceeding PCa mortality [845]. Several studies showed that ADT, after only six months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [846]. The RTOG 92-02 [847] and 94-08 [415] trials confirmed an increased cardiovascular risk, unrelated to the duration of ADT and not accompanied by an overall increased cardiovascular mortality. No increase in cardiovascular mortality has been reported in a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 or EORTC 22863 [848]. However, an increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [849] or presenting with a metabolic syndrome [850].

It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [851]. However, the methodology used in these studies does not provide convincing evidence to show a clear superiority of these compounds.

These data resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [689]. Preventive advice includes non-specific measures such as loss of

weight, increased exercise, improved nutrition and smoking cessation.

8.2.4.7 Fatigue

Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure [852, 853], with prolonged efficacy [854] and improved specific survival [855].

Anaemia may be a cause of fatigue. Anaemia requires an etiological diagnosis (medullar invasion, mainly inflammatory, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Iron supplementation (using injectable formulations only) must be systematic if deficiency is observed. Regular blood transfusions are required if severe anaemia is present. Erythropoiesis-stimulating agents might be considered in dedicated cases, taking into account the possible increased risk of thrombovascular events [856].

8.2.4.8 neurological side effects

Castration seems also to be associated with an increased risk of stroke [857], and is suspect to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [858].

8.3 Overall quality of life in men with prostate cancer

Living longer with prostate cancer, does not necessarily equate to living well [803, 762]. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for prostate cancer [859]. Radical treatment for prostate cancer can negatively impact long-term QoL (e.g. sexual, urinary and bowel dysfunction), as can ADT used in short or long-term treatment e.g. loss of muscle mass, sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae increased cardiovascular and bone fracture risk [860, 861]. Direct symptoms from advanced or metastatic cancer e.g. pain, hypercalcaemia, spinal cord compression, pathological fractures, also adversely affect health [862, 863]. Men's QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [864, 865].

The concept of 'quality of life' is subjective and can mean different things to different men, but there are some generally common features across virtually all patients. Drawing from these common features, specific tools or 'patient reported outcome measures' (PROMs) have been developed and validated for men with prostate cancer. These questionnaires assess common issues that affect men after prostate cancer diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. During the process of undertaking two dedicated SRs around cancer-specific QoL outcomes in men with PCa as the foundation for our guideline recommendations, the following validated PROMs were found in our searches (see Table 8.3.1).

Table 8.3.1: PROMs assessing cancer specific quality of life

Questionnaire	Domains / items
Functional Assessment of Cancer Therapy-General (FACT-G) [866]	Physical well-being, Social/family well-being, Emotional well-being, and Functional well-being.
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [867]	12 cancer site specific items to assess for prostate related symptoms. Can be combined with FACT-G or reported separately.
European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [868]	Five functional scales (physical, role, cognitive, emotional, and social); Three symptom scales (fatigue, pain, and nausea and vomiting); Global health status / QoL scale; and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.
European Organisation for Research and Treatment of Cancer QLQ-PR 25 (EORTC QLQ-PR 25) [869]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Expanded prostate cancer index composite (EPIC) [870]	Urinary, bowel, sexual, and hormonal symptoms.
Expanded prostate cancer index composite short form 26 (EPIC 26) [871]	Urinary, sexual, bowel, and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [872]	Urinary, bowel, and sexual domains.

Prostate Cancer Quality of Life Instrument (PCQoL) [873]	Urinary, sexual, and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instrument [874]	Urinary, bowel, and sexual domains.

8.3.1 Long-term (≥ 12 months) quality of life outcomes in men with localised disease.

Men undergoing local treatments

Recently the results of the Prostate Testing for Cancer and Treatment (ProtecT) trial ($n = 1,643$ men) were published [875]. The study reported no difference in EORTC QLQ-C30 assessed global QoL, up to five years of follow-up in men aged 50-69 years with T1-T2 disease randomised for treatment with AM, RP or RT [875]. However, EPIC urinary summary scores (at 6 years) were worse in men treated with RP compared to AM or RT (88.7 vs. 89.0 vs. 91.4, respectively) as were urinary incontinence (80.9 vs. 85.8 vs. 89.4, respectively) and sexual summary, function and bother scores (32.3 vs. 40.6 vs. 41.3 for sexual summary, 23.7 vs. 32.5 vs. 32.7 for sexual function and 51.4 vs. 57.9 vs. 60.1 for sexual bother, respectively) at six years of follow-up. Minimal clinically important differences for the 50 item EPIC questionnaire are not to our knowledge available. For men receiving RT, EPIC bowel scores were poorer compared to AM and RP in all domains: function (90.8 vs. 92.3 vs. 92.3, respectively), bother (91.7 vs. 94.2 vs. 93.7, respectively) and summary (91.2 vs. 93.2 vs. 93.0, respectively) at six years of follow-up in the ProtecT trial.

The findings regarding RP and RT are supported by other observational studies, the most important being The Prostate Cancer Outcomes Study (PCOS) [876] that studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT. The study reported that at five years of follow-up, men who underwent RP had a higher prevalence of urinary incontinence and ED, while men treated with RT had a higher prevalence of bowel dysfunction. However, despite these differences detected at five years, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between RP and RT at fifteen years.

With respect to brachytherapy cancer-specific QoL outcomes, the best available evidence come from one small RCT ($n = 200$) evaluating bilateral nerve sparing RP and brachytherapy in men with localised disease (up to T2a), which reported worsening of physical functioning as well as irritative urinary symptomatology in 20% of brachytherapy patients at one year of follow-up. However, there were no significant differences in EORTC-QLQ-C30/PR-25 scores at five years of follow-up when comparing to pre-treatment values [877]. It should be noted of this trial within group tests only were reported.

Recommendations	LE	GR
Advise eligible patients for active surveillance, that global quality of life is equivalent for up to five years compared to radical prostatectomy or radiotherapy.	1b	A
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of radiotherapy on bowel function with patients.	1b	A
Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after five years.	1b	C

8.3.2 Improving quality of life in men who have been diagnosed with prostate cancer

Men undergoing local treatments

In men with localised disease, nurse led multi-disciplinary rehabilitation (addressing sexual functioning, cancer worry, dyadic adjustment, depression, managing bowel and urinary function problems) provided positive short-term effects (four months) on sexual function (effect size 0.45) and long-term (twelve months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [878].

The use of PDE5 inhibitors in penile rehabilitation has been subject to some debate. A single centre, double blind RCT of 100 men undergoing nerve-sparing surgery reported no benefit of nightly sildenafil (50 mg) compared to on-demand use [405]. However, a multi-centre double blind RCT ($n = 423$) in men aged < 68 years, with normal pre-treatment erectile function undergoing either open, conventional or robot assisted laparoscopic nerve-sparing RP, Tadalafil (5 mg) once per day improved participants EPIC sexual domain-scores (least squares mean difference +9.6; 95% CI: 3.1-16.0) when compared to 20 mg 'on demand' or placebo at nine months of follow-up [406]. Therefore, based on discordant results, no clear recommendation is possible, even if a trend exists for early use of PDE5 inhibitors after RP for penile rehabilitation. A detailed discussion can be found in the EAU Male Sexual Dysfunction Guidelines [879].

Men undergoing systemic treatments

Similar to men treated with a radical approach (see above) men with T1-T3 disease undergoing RT and ADT a combined nurse led psychological support and physiotherapist led multi-disciplinary rehabilitation has reported

improvements in QoL. Specifically this intervention involved action planning around patients' needs related to lifestyle changes, weight control, toilet habits, sexuality, and psychological problems. This was complemented with pelvic floor muscle therapy. Improvements in urinary (adjusted mean 4.5: 95% CI 0.6-8.4), irritative (adjusted mean 5.8: 95% CI: 1.4-10.3) and hormonal (adjusted mean 4.8: 95% CI: 0.8-8.8) EPIC domains were found up to 22 weeks of follow-up [880].

Providing supervised aerobic and resistance exercise training of a moderate intensity improves EORTC QLQ-C30 role (adjusted mean 15.8: 95% CI: 6.6-24.9) and cognitive domain outcomes (adjusted mean 11.4: 95% CI: 3.3-19.6) as well as symptom scales for fatigue (adjusted mean -11.0: 95% CI: -20.2,-1.7), nausea (adjusted mean -4.0: 95% CI: -7.4,-0.25), and dyspnoea (adjusted mean -12.4: 95% CI: -22.5,-2.3) up to three months in men treated with ADT [852]. Such interventions have also reported clinically relevant improvements in FACT-P (mean difference 8.9: 95% CI: 3.7-14.2) in men on long-term ADT [881, 882]. These findings are supported by a recent SR which reported improvements up to twelve weeks in cancer-specific QoL in a meta-analysis of high quality trials (SMD 0.33: 95% CI: 0.08-0.58) [883].

Recommendations	LE	GR
Offer men on androgen deprivation therapy, twelve weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	1a	A
Offer men with T1-T3 disease specialist nurse led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	1b	A

9. REFERENCES

- Mottet, N., *et al.* EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27568654>
- Cornford, P., *et al.* EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. *Eur Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27591931>
- Moldovan P., *et al.* What is the performance of prostate pre-biopsy multi parametric MRI in predicting prostate biopsy results?. PROSPERO International prospective register of systematic reviews, 2015.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015021929
- Fossati, N., *et al.* The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review. *Eur Urol*, 2017.
<https://www.ncbi.nlm.nih.gov/pubmed/28126351>
- Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
- Van den Broeck T., *et al.* How does biochemical recurrence following curative treatment for prostate cancer impact on overall survival, cancer-specific survival and development of metastatic disease?. PROSPERO International prospective register of systematic reviews, 2015.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015026807
- Ferlay, J., *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, 2015. 136: E359.
<https://www.ncbi.nlm.nih.gov/pubmed/25220842>
- Haas, G.P., *et al.* The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *Can J Urol*, 2008. 15: 3866.
<https://www.ncbi.nlm.nih.gov/pubmed/18304396>
- Bell, K.J., *et al.* Prevalence of incidental prostate cancer: A systematic review of autopsy studies. *Int J Cancer*, 2015. 137: 1749.
<https://www.ncbi.nlm.nih.gov/pubmed/25821151>
- Jansson, K.F., *et al.* Concordance of tumor differentiation among brothers with prostate cancer. *Eur Urol*, 2012. 62: 656.
<https://www.ncbi.nlm.nih.gov/pubmed/22386193>
- Hemminki, K. Familial risk and familial survival in prostate cancer. *World J Urol*, 2012. 30: 143.

- <https://www.ncbi.nlm.nih.gov/pubmed/22116601>
12. Randazzo, M., *et al.* A positive family history as a risk factor for prostate cancer in a population-based study with organised prostate-specific antigen screening: results of the Swiss European Randomised Study of Screening for Prostate Cancer (ERSPC, Aarau). *BJU Int*, 2016. 117: 576.
<https://www.ncbi.nlm.nih.gov/pubmed/26332304>
 13. Tan, D.S., *et al.* Cancer Genomics: Diversity and Disparity Across Ethnicity and Geography. *J Clin Oncol*, 2016. 34: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/26578615>
 14. Eeles, R.A., *et al.* Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. *Nat Genet*, 2013. 45: 385.
<https://www.ncbi.nlm.nih.gov/pubmed/23535732>
 15. Amin Al Olama, A., *et al.* Multiple novel prostate cancer susceptibility signals identified by fine-mapping of known risk loci among Europeans. *Hum Mol Genet*, 2015. 24: 5589.
<https://www.ncbi.nlm.nih.gov/pubmed/26025378>
 16. Pritchard, C.C., *et al.* Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *N Engl J Med*, 2016. 375: 443.
<https://www.ncbi.nlm.nih.gov/pubmed/27433846>
 17. Lynch, H.T., *et al.* Screening for familial and hereditary prostate cancer. *Int J Cancer*, 2016. 138: 2579.
<https://www.ncbi.nlm.nih.gov/pubmed/26638190>
 18. Ewing, C.M., *et al.* Germline mutations in HOXB13 and prostate-cancer risk. *N Engl J Med*, 2012. 366: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/22236224>
 19. Bancroft, E.K., *et al.* Targeted Prostate Cancer Screening in BRCA1 and BRCA2 Mutation Carriers: Results from the Initial Screening Round of the IMPACT Study. *Eur Urol*, 2014. 66: 489.
<https://www.ncbi.nlm.nih.gov/pubmed/24484606>
 20. Breslow, N., *et al.* Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France. *Int J Cancer*, 1977. 20: 680.
<https://www.ncbi.nlm.nih.gov/pubmed/924691>
 21. Leitzmann, M.F., *et al.* Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. *Clin Epidemiol*, 2012. 4: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/22291478>
 22. Esposito, K., *et al.* Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. *J Endocrinol Invest*, 2013. 36: 132.
<https://www.ncbi.nlm.nih.gov/pubmed/23481613>
 23. Blanc-Lapierre, A., *et al.* Metabolic syndrome and prostate cancer risk in a population-based case-control study in Montreal, Canada. *BMC Public Health*, 2015. 15: 913.
<https://www.ncbi.nlm.nih.gov/pubmed/26385727>
 24. Preston, M.A., *et al.* Metformin use and prostate cancer risk. *Eur Urol*, 2014. 66: 1012.
<https://www.ncbi.nlm.nih.gov/pubmed/24857538>
 25. Freedland, S.J., *et al.* Statin use and risk of prostate cancer and high-grade prostate cancer: results from the REDUCE study. *Prostate Cancer Prostatic Dis*, 2013. 16: 254.
<https://www.ncbi.nlm.nih.gov/pubmed/23567655>
 26. YuPeng, L., *et al.* Cholesterol Levels in Blood and the Risk of Prostate Cancer: A Meta-analysis of 14 Prospective Studies. *Cancer Epidemiol Biomarkers Prev*, 2015. 24: 1086.
<https://www.ncbi.nlm.nih.gov/pubmed/25953767>
 27. Vidal, A.C., *et al.* Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. *Cancer Epidemiol Biomarkers Prev*, 2014. 23: 2936.
<https://www.ncbi.nlm.nih.gov/pubmed/25261967>
 28. Davies, N.M., *et al.* The effects of height and BMI on prostate cancer incidence and mortality: a Mendelian randomization study in 20,848 cases and 20,214 controls from the PRACTICAL consortium. *Cancer Causes Control*, 2015. 26: 1603.
<https://www.ncbi.nlm.nih.gov/pubmed/26387087>
 29. Dickerman, B.A., *et al.* Alcohol intake, drinking patterns, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. *Cancer Causes Control*, 2016. 27: 1049.
<https://www.ncbi.nlm.nih.gov/pubmed/27351919>
 30. Key, T.J. Nutrition, hormones and prostate cancer risk: results from the European prospective investigation into cancer and nutrition. *Recent Results Cancer Res*, 2014. 202: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/24531775>

31. Alexander, D.D., *et al.* Meta-Analysis of Long-Chain Omega-3 Polyunsaturated Fatty Acids (LComega-3PUFA) and Prostate Cancer. *Nutr Cancer*, 2015. 67: 543.
<https://www.ncbi.nlm.nih.gov/pubmed/25826711>
32. Lippi, G., *et al.* Fried food and prostate cancer risk: systematic review and meta-analysis. *Int J Food Sci Nutr*, 2015. 66: 587.
<https://www.ncbi.nlm.nih.gov/pubmed/26114920>
33. Chen, P., *et al.* Lycopene and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis. *Medicine (Baltimore)*, 2015. 94: e1260.
<https://www.ncbi.nlm.nih.gov/pubmed/26287411>
34. Ilic, D., *et al.* Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review. *Maturitas*, 2012. 72: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/22633187>
35. Bylsma, L.C., *et al.* A review and meta-analysis of prospective studies of red and processed meat, meat cooking methods, heme iron, heterocyclic amines and prostate cancer. *Nutr J*, 2015. 14: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/26689289>
36. Kristal, A.R., *et al.* Plasma vitamin D and prostate cancer risk: results from the Selenium and Vitamin E Cancer Prevention Trial. *Cancer Epidemiol Biomarkers Prev*, 2014. 23: 1494.
<https://www.ncbi.nlm.nih.gov/pubmed/24732629>
37. Nyame, Y.A., *et al.* Associations Between Serum Vitamin D and Adverse Pathology in Men Undergoing Radical Prostatectomy. *J Clin Oncol*, 2016. 34: 1345.
<https://www.ncbi.nlm.nih.gov/pubmed/26903577>
38. Lippman, S.M., *et al.* Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*, 2009. 301: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/19066370>
39. Kramer, B.S., *et al.* Use of 5-alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Clin Oncol*, 2009. 27: 1502.
<https://www.ncbi.nlm.nih.gov/pubmed/19252137>
40. Andriole, G.L., *et al.* Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*, 2010. 362: 1192.
<https://www.ncbi.nlm.nih.gov/pubmed/20357281>
41. Thompson, I.M., *et al.* The influence of finasteride on the development of prostate cancer. *N Engl J Med*, 2003. 349: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/19297565>
42. Haider, A., *et al.* Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. *J Urol*, 2015. 193: 80.
<https://www.ncbi.nlm.nih.gov/pubmed/24980615>
43. Zhou, C.K., *et al.* Male Pattern Baldness in Relation to Prostate Cancer-Specific Mortality: A Prospective Analysis in the NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol*, 2016. 183: 210.
<https://www.ncbi.nlm.nih.gov/pubmed/26764224>
44. Lian, W.Q., *et al.* Gonorrhea and Prostate Cancer Incidence: An Updated Meta-Analysis of 21 Epidemiologic Studies. *Med Sci Monit*, 2015. 21: 1902.
<https://www.ncbi.nlm.nih.gov/pubmed/26126881>
45. Rao, D., *et al.* Does night-shift work increase the risk of prostate cancer? a systematic review and meta-analysis. *Onco Targets Ther*, 2015. 8: 2817.
<https://www.ncbi.nlm.nih.gov/pubmed/26491356>
46. Raslau, D., *et al.* The risk of prostate cancer in pilots: a meta-analysis. *Aerosp Med Hum Perform*, 2015. 86: 112.
<https://www.ncbi.nlm.nih.gov/pubmed/25946735>
47. Islami, F., *et al.* A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies. *Eur Urol*, 2014. 66: 1054.
<https://www.ncbi.nlm.nih.gov/pubmed/25242554>
48. Zhang, X.L., *et al.* Vasectomy and the risk of prostate cancer: a meta-analysis of cohort studies. *Int J Clin Exp Med*, 2015. 8: 17977.
<https://www.ncbi.nlm.nih.gov/pubmed/26770392>
49. Cremers, R.G., *et al.* Self-reported acne is not associated with prostate cancer. *Urol Oncol*, 2014. 32: 941.
<https://www.ncbi.nlm.nih.gov/pubmed/25011577>

50. Huang, T.B., *et al.* Aspirin use and the risk of prostate cancer: a meta-analysis of 24 epidemiologic studies. *Int Urol Nephrol*, 2014. 46: 1715.
<https://www.ncbi.nlm.nih.gov/pubmed/24687637>
51. Bhindi, B., *et al.* The impact of the use of aspirin and other nonsteroidal anti-inflammatory drugs on the risk of prostate cancer detection on biopsy. *Urology*, 2014. 84: 1073.
<https://www.ncbi.nlm.nih.gov/pubmed/25443907>
52. Lin, S.W., *et al.* Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. *Int J Cancer*, 2012. 131: E1015.
<https://www.ncbi.nlm.nih.gov/pubmed/22539073>
53. Pabalan, N., *et al.* Association of male circumcision with risk of prostate cancer: a meta-analysis. *Prostate Cancer Prostatic Dis*, 2015. 18: 352.
<https://www.ncbi.nlm.nih.gov/pubmed/26215783>
54. Rider, J.R., *et al.* Ejaculation Frequency and Risk of Prostate Cancer: Updated Results with an Additional Decade of Follow-up. *Eur Urol*, 2016. 70: 974.
<https://www.ncbi.nlm.nih.gov/pubmed/27033442>
55. Brierley, A., *et al.*, TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. 20016.
<http://www.uicc.org/resources/tnm/publications-resources>
56. Cooperberg, M.R., *et al.* The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *J Urol*, 2005. 173: 1938.
<https://www.ncbi.nlm.nih.gov/pubmed/15879786>
57. Epstein, J.I., *et al.* The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*, 2005. 29: 1228.
<https://www.ncbi.nlm.nih.gov/pubmed/16096414>
58. Epstein, J.I., *et al.* The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26492179>
59. Epstein, J.I., *et al.* A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. *Eur Urol*, 2016. 69: 428.
<https://www.ncbi.nlm.nih.gov/pubmed/26166626>
60. Zumsteg, Z.S., *et al.* A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol*, 2013. 64: 895.
[http://www.europeanurology.com/article/S0302-2838\(13\)00257-1/](http://www.europeanurology.com/article/S0302-2838(13)00257-1/)
61. IARC France All Cancers (excluding non-melanoma skin cancer) Estimated Incidence, Mortality and Prevalence Worldwide in 2012. 2014.
http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
62. Etzioni, R., *et al.* Limitations of basing screening policies on screening trials: The US Preventive Services Task Force and Prostate Cancer Screening. *Med Care*, 2013. 51: 295.
<https://www.ncbi.nlm.nih.gov/pubmed/23269114>
63. Ilic, D., *et al.* Screening for prostate cancer. *Cochrane Database Syst Rev*, 2013. 1: CD004720.
<https://www.ncbi.nlm.nih.gov/pubmed/23440794>
64. Loeb, S. Guideline of guidelines: prostate cancer screening. *BJU Int*, 2014. 114: 323.
<https://www.ncbi.nlm.nih.gov/pubmed/>
65. Andriole, G.L., *et al.* Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*, 2009. 360: 1310.
<https://www.ncbi.nlm.nih.gov/pubmed/19297565>
66. Schroder, F.H., *et al.* Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*, 2009. 360: 1320.
<https://www.ncbi.nlm.nih.gov/pubmed/24981126>
67. Hugosson, J., *et al.* Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol*, 2010. 11: 725.
<https://www.ncbi.nlm.nih.gov/pubmed/20598634>
68. Carter, H.B., *et al.* Early detection of prostate cancer: AUA Guideline. *J Urol*, 2013. 190: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/23659877>
69. Chou, R., *et al.* Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*, 2011. 155: 762.
<https://www.ncbi.nlm.nih.gov/pubmed/21984740>

70. Auffenberg, G.B., *et al.* Application of the 2013 American Urological Association early detection of prostate cancer guideline: who will we miss? *World J Urol*, 2014. 32: 959.
<https://www.ncbi.nlm.nih.gov/pubmed/24946729>
71. Banerji, J.S., *et al.* Prostate Needle Biopsy Outcomes in the Era of the U.S. Preventive Services Task Force Recommendation against Prostate Specific Antigen Based Screening. *J Urol*, 2016. 195: 66.
<https://www.ncbi.nlm.nih.gov/pubmed/26254722>
72. Arnsrud Godtman, R., *et al.* Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Goteborg randomized population-based prostate cancer screening trial. *Eur Urol*, 2015. 68: 354.
<https://www.ncbi.nlm.nih.gov/pubmed/25556937>
73. Hayes, J.H., *et al.* Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. *JAMA*, 2014. 311: 1143.
<https://www.ncbi.nlm.nih.gov/pubmed/24643604>
74. Booth, N., *et al.* Health-related quality of life in the Finnish trial of screening for prostate cancer. *Eur Urol*, 2014. 65: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/23265387>
75. Vasarainen, H., *et al.* Effects of prostate cancer screening on health-related quality of life: results of the Finnish arm of the European randomized screening trial (ERSPC). *Acta Oncol*, 2013. 52: 1615.
<https://www.ncbi.nlm.nih.gov/pubmed/23786174>
76. Heijnsdijk, E.A., *et al.* Quality-of-life effects of prostate-specific antigen screening. *N Engl J Med*, 2012. 367: 595.
<https://www.ncbi.nlm.nih.gov/pubmed/22894572>
77. Schroder, F.H., *et al.* Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*, 2014. 384: 2027.
<https://www.ncbi.nlm.nih.gov/pubmed/25108889>
78. The benefits and harms of breast cancer screening: an independent review. *Lancet*, 2012. 380: 1778.
<https://www.ncbi.nlm.nih.gov/pubmed/23117178>
79. Albright, F., *et al.* Prostate cancer risk prediction based on complete prostate cancer family history. *Prostate*, 2015. 75: 390.
<https://www.ncbi.nlm.nih.gov/pubmed/25408531>
80. Kamangar, F., *et al.* Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*, 2006. 24: 2137.
<https://www.ncbi.nlm.nih.gov/pubmed/16682732>
81. Vickers, A.J., *et al.* Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. *BMJ*, 2013. 346: f2023.
<https://www.ncbi.nlm.nih.gov/pubmed/23596126>
82. Carlsson, S., *et al.* Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. *Bmj*, 2014. 348: g2296.
<https://www.ncbi.nlm.nih.gov/pubmed/24682399>
83. Gulati, R., *et al.* Screening Men at Increased Risk for Prostate Cancer Diagnosis: Model Estimates of Benefits and Harms. *Cancer Epidemiol Biomarkers Prev*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27742670>
84. Vedder, M.M., *et al.* The added value of percentage of free to total prostate-specific antigen, PCA3, and a kallikrein panel to the ERSPC risk calculator for prostate cancer in prescreened men. *Eur Urol*, 2014. 66: 1109.
<https://www.ncbi.nlm.nih.gov/pubmed/25168616>
85. Leyten, G.H., *et al.* Prospective multicentre evaluation of PCA3 and TMPRSS2-ERG gene fusions as diagnostic and prognostic urinary biomarkers for prostate cancer. *Eur Urol*, 2014. 65: 534.
<https://www.ncbi.nlm.nih.gov/pubmed/23201468>
86. Boegemann, M., *et al.* The percentage of prostate-specific antigen (PSA) isoform [-2]proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men aged ≤ 65 years. *BJU Int*, 2016. 117: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/25818705>
87. Bryant, R.J., *et al.* Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. *J Natl Cancer Inst*, 2015. 107.
<https://www.ncbi.nlm.nih.gov/pubmed/25863334>

88. Louie, K.S., *et al.* Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. *Ann Oncol*, 2015. 26: 848.
<https://www.ncbi.nlm.nih.gov/pubmed/25403590>
89. Loeb, S., *et al.* Pathological characteristics of prostate cancer detected through prostate specific antigen based screening. *J Urol*, 2006. 175: 902.
<https://www.ncbi.nlm.nih.gov/pubmed/16469576>
90. Gelfond, J., *et al.* Intermediate-Term Risk of Prostate Cancer is Directly Related to Baseline Prostate Specific Antigen: Implications for Reducing the Burden of Prostate Specific Antigen Screening. *J Urol*, 2015. 194: 46.
<https://www.ncbi.nlm.nih.gov/pubmed/25686543>
91. Droz, J.P., *et al.* Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. *Lancet Oncol*, 2014. 15: e404.
<https://www.ncbi.nlm.nih.gov/pubmed/25079103>
92. Richie, J.P., *et al.* Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology*, 1993. 42: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/7692657>
93. Carvalhal, G.F., *et al.* Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. *J Urol*, 1999. 161: 835.
<https://www.ncbi.nlm.nih.gov/pubmed/10022696>
94. Okotie, O.T., *et al.* Characteristics of prostate cancer detected by digital rectal examination only. *Urology*, 2007. 70: 1117.
<https://www.ncbi.nlm.nih.gov/pubmed/18158030>
95. Gosselaar, C., *et al.* The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. *Eur Urol*, 2008. 54: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/18423977>
96. Stamey, T.A., *et al.* Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med*, 1987. 317: 909.
<https://www.ncbi.nlm.nih.gov/pubmed/2442609>
97. Catalona, W.J., *et al.* Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol*, 1994. 151: 1283.
<https://www.ncbi.nlm.nih.gov/pubmed/7512659>
98. Semjonow, A., *et al.* Discordance of assay methods creates pitfalls for the interpretation of prostate-specific antigen values. *Prostate Suppl*, 1996. 7: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/8950358>
99. Thompson, I.M., *et al.* Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med*, 2004. 350: 2239.
<https://www.ncbi.nlm.nih.gov/pubmed/15163773>
100. Dong, F., *et al.* Validation of pretreatment nomograms for predicting indolent prostate cancer: efficacy in contemporary urological practice. *J Urol*, 2008. 180: 150.
<https://www.ncbi.nlm.nih.gov/pubmed/18485398>
101. Carter, H.B., *et al.* Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA*, 1992. 267: 2215.
<https://www.ncbi.nlm.nih.gov/pubmed/1372942>
102. Schmid, H.P., *et al.* Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. *Cancer*, 1993. 71: 2031.
<https://www.ncbi.nlm.nih.gov/pubmed/7680277>
103. Arlen, P.M., *et al.* Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. *J Urol*, 2008. 179: 2181.
<https://www.ncbi.nlm.nih.gov/pubmed/18423743>
104. Heidenreich, A. Identification of high-risk prostate cancer: role of prostate-specific antigen, PSA doubling time, and PSA velocity. *Eur Urol*, 2008. 54: 976.
<https://www.ncbi.nlm.nih.gov/pubmed/18640768>
105. Ramirez, M.L., *et al.* Current applications for prostate-specific antigen doubling time. *Eur Urol*, 2008. 54: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/18439749>

106. O'Brien, M.F., *et al.* Pretreatment prostate-specific antigen (PSA) velocity and doubling time are associated with outcome but neither improves prediction of outcome beyond pretreatment PSA alone in patients treated with radical prostatectomy. *J Clin Oncol*, 2009. 27: 3591.
<https://www.ncbi.nlm.nih.gov/pubmed/19506163>
107. Vickers, A.J., *et al.* Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. *J Clin Oncol*, 2009. 27: 398.
<https://www.ncbi.nlm.nih.gov/pubmed/19064972>
108. Catalona, W.J., *et al.* Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *JAMA*, 1998. 279: 1542.
<https://www.ncbi.nlm.nih.gov/pubmed/9605898>
109. Stephan, C., *et al.* The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients with prostate carcinoma and benign prostate hyperplasia. *Cancer*, 1997. 79: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/8988733>
110. Loeb, S., *et al.* The Prostate Health Index: a new test for the detection of prostate cancer. *Ther Adv Urol*, 2014. 6: 74.
<https://www.ncbi.nlm.nih.gov/pubmed/24688603>
111. de la Calle, C., *et al.* Multicenter Evaluation of the Prostate Health Index to Detect Aggressive Prostate Cancer in Biopsy Naive Men. *J Urol*, 2015. 194: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/25636659>
112. Nordstrom, T., *et al.* Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer. *Eur Urol*, 2015. 68: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/25151013>
113. Deras, I.L., *et al.* PCA3: a molecular urine assay for predicting prostate biopsy outcome. *J Urol*, 2008. 179: 1587.
<https://www.ncbi.nlm.nih.gov/pubmed/18295257>
114. Hessels, D., *et al.* DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. *Eur Urol*, 2003. 44: 8.
<https://www.ncbi.nlm.nih.gov/pubmed/12814669>
115. Nakanishi, H., *et al.* PCA3 molecular urine assay correlates with prostate cancer tumor volume: implication in selecting candidates for active surveillance. *J Urol*, 2008. 179: 1804.
<https://www.ncbi.nlm.nih.gov/pubmed/18353398>
116. Hessels, D., *et al.* Predictive value of PCA3 in urinary sediments in determining clinico-pathological characteristics of prostate cancer. *Prostate*, 2010. 70: 10.
<https://www.ncbi.nlm.nih.gov/pubmed/19708043>
117. Auprich, M., *et al.* Contemporary role of prostate cancer antigen 3 in the management of prostate cancer. *Eur Urol*, 2011. 60: 1045.
<https://www.ncbi.nlm.nih.gov/pubmed/21871709>
118. Nicholson, A., *et al.* The clinical effectiveness and cost-effectiveness of the PROGENSA(R) prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation. *Health Technol Assess*, 2015. 19: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/26507078>
119. Roobol, M.J., *et al.* A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur Urol*, 2010. 57: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/19733959>
120. Eastham, J.A., *et al.* Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. *JAMA*, 2003. 289: 2695.
<https://www.ncbi.nlm.nih.gov/pubmed/12771116>
121. Stephan, C., *et al.* Interchangeability of measurements of total and free prostate-specific antigen in serum with 5 frequently used assay combinations: an update. *Clin Chem*, 2006. 52: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/16391327>
122. Eggener, S.E., *et al.* Empiric antibiotics for an elevated prostate-specific antigen (PSA) level: a randomised, prospective, controlled multi-institutional trial. *BJU Int*, 2013. 112: 925.
<https://www.ncbi.nlm.nih.gov/pubmed/23890317>
123. Hara, R., *et al.* Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. *Urology*, 2008. 71: 191.
<https://www.ncbi.nlm.nih.gov/pubmed/18308081>

124. Takenaka, A., *et al.* A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. *Prostate Cancer Prostatic Dis*, 2008. 11: 134. <https://www.ncbi.nlm.nih.gov/pubmed/17533394>
125. Epstein, J.I., *et al.* Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. *J Urol*, 2006. 175: 820. <https://www.ncbi.nlm.nih.gov/pubmed/16469560>
126. Merrimen, J.L., *et al.* Multifocal high grade prostatic intraepithelial neoplasia is a significant risk factor for prostatic adenocarcinoma. *J Urol*, 2009. 182: 485. <https://www.ncbi.nlm.nih.gov/pubmed/19524976>
127. Kronz, J.D., *et al.* High-grade prostatic intraepithelial neoplasia with adjacent small atypical glands on prostate biopsy. *Hum Pathol*, 2001. 32: 389. <https://www.ncbi.nlm.nih.gov/pubmed/11331955>
128. Guo, C.C., *et al.* Intraductal carcinoma of the prostate on needle biopsy: Histologic features and clinical significance. *Mod Pathol*, 2006. 19: 1528. <https://www.ncbi.nlm.nih.gov/pubmed/16980940>
129. Partin, A.W., *et al.* Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. *J Urol*, 2014. 192: 1081. <https://www.ncbi.nlm.nih.gov/pubmed/24747657>
130. Moore, C.K., *et al.* Prognostic significance of high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation in the contemporary era. *J Urol*, 2005. 173: 70. <https://www.ncbi.nlm.nih.gov/pubmed/15592031>
131. Walz, J., *et al.* High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. *Eur Urol*, 2006. 50: 498. <https://www.ncbi.nlm.nih.gov/pubmed/16631303>
132. Moran, B.J., *et al.* Re-biopsy of the prostate using a stereotactic transperineal technique. *J Urol*, 2006. 176: 1376. <https://www.ncbi.nlm.nih.gov/pubmed/16952636>
133. Donovan, J., *et al.* Prostate Testing for Cancer and Treatment (ProtecT) feasibility study. *Health Technol Assess*, 2003. 7: 1. <https://www.ncbi.nlm.nih.gov/pubmed/12709289>
134. Eichler, K., *et al.* Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol*, 2006. 175: 1605. <https://www.ncbi.nlm.nih.gov/pubmed/16600713>
135. Shariat, S.F., *et al.* Using biopsy to detect prostate cancer. *Rev Urol*, 2008. 10: 262. <https://www.ncbi.nlm.nih.gov/pubmed/19145270>
136. Zigeuner, R., *et al.* Detection of prostate cancer by TURP or open surgery in patients with previously negative transrectal prostate biopsies. *Urology*, 2003. 62: 883. <https://www.ncbi.nlm.nih.gov/pubmed/14624913>
137. Linzer, D.G., *et al.* Seminal vesicle biopsy: accuracy and implications for staging of prostate cancer. *Urology*, 1996. 48: 757. <https://www.ncbi.nlm.nih.gov/pubmed/8911521>
138. Pelzer, A.E., *et al.* Are transition zone biopsies still necessary to improve prostate cancer detection? Results from the tyrol screening project. *Eur Urol*, 2005. 48: 916. <https://www.ncbi.nlm.nih.gov/pubmed/16126324>
139. Aron, M., *et al.* Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. *BJU Int*, 2000. 85: 682. <https://www.ncbi.nlm.nih.gov/pubmed/10759665>
140. Cuevas, O., *et al.* Significant ecological impact on the progression of fluoroquinolone resistance in *Escherichia coli* with increased community use of moxifloxacin, levofloxacin and amoxicillin/ clavulanic acid. *J Antimicrob Chemother*, 2011. 66: 664. <https://www.ncbi.nlm.nih.gov/pubmed/21172788>
141. Loeb, S., *et al.* Complications after prostate biopsy: data from SEER-Medicare. *J Urol*, 2011. 186: 1830. <https://www.ncbi.nlm.nih.gov/pubmed/21944136>
142. von Knobloch, R., *et al.* Bilateral fine-needle administered local anaesthetic nerve block for pain control during TRUS-guided multi-core prostate biopsy: a prospective randomised trial. *Eur Urol*, 2002. 41: 508. <https://www.ncbi.nlm.nih.gov/pubmed/12074792>

143. Adamakis, I., *et al.* Pain during transrectal ultrasonography guided prostate biopsy: a randomized prospective trial comparing periprostatic infiltration with lidocaine with the intrarectal instillation of lidocaine-prilocain cream. *World J Urol*, 2004. 22: 281.
<https://www.ncbi.nlm.nih.gov/pubmed/14689224>
144. NCCN Clinical practice Guidelines in Oncology™: Prostate Cancer Early Detection, Version 2. 2015. 2015.
https://www.nccn.org/professionals/physician_gls/f_guidelines.asp
145. Loeb, S., *et al.* Systematic review of complications of prostate biopsy. *Eur Urol*, 2013. 64: 876.
<https://www.ncbi.nlm.nih.gov/pubmed/23787356>
146. Giannarini, G., *et al.* Continuing or discontinuing low-dose aspirin before transrectal prostate biopsy: results of a prospective randomized trial. *Urology*, 2007. 70: 501.
<https://www.ncbi.nlm.nih.gov/pubmed/17688919>
147. Garcia C, Does transperineal prostate biopsy reduce complications compared with transrectal biopsy? a systematic review and meta-analysis of randomised controlled trials. 2016. 195:4 SUPPL. 1 p. e328.
148. Smeenge, M., *et al.* Role of transrectal ultrasonography (TRUS) in focal therapy of prostate cancer: report from a Consensus Panel. *BJU Int*, 2012. 110: 942.
<https://www.ncbi.nlm.nih.gov/pubmed/22462566>
149. Turkbey, B., *et al.* Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. *J Urol*, 2011. 186: 1818.
<https://www.ncbi.nlm.nih.gov/pubmed/21944089>
150. Selnaes, K.M., *et al.* Peripheral zone prostate cancer localization by multiparametric magnetic resonance at 3 T: unbiased cancer identification by matching to histopathology. *Invest Radiol*, 2012. 47: 624.
<https://www.ncbi.nlm.nih.gov/pubmed/23011187>
151. Bratan, F., *et al.* Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. *Eur Radiol*, 2013. 23: 2019.
<https://www.ncbi.nlm.nih.gov/pubmed/23494494>
152. Le, J.D., *et al.* Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. *Eur Urol*, 2015. 67: 569.
<https://www.ncbi.nlm.nih.gov/pubmed/25257029>
153. Fütterer, J.J., *et al.* Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. *Eur Urol*, 2015. 68: 1045.
<https://www.ncbi.nlm.nih.gov/pubmed/25656808>
154. van Hove, A., *et al.* Comparison of image-guided targeted biopsies versus systematic randomized biopsies in the detection of prostate cancer: a systematic literature review of well-designed studies. *World J Urol*, 2014. 32: 847.
<https://www.ncbi.nlm.nih.gov/pubmed/24919965>
155. Schoots, I.G., *et al.* Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. *Eur Urol*, 2015. 68: 438.
<https://www.ncbi.nlm.nih.gov/pubmed/25480312>
156. Valerio, M., *et al.* Detection of Clinically Significant Prostate Cancer Using Magnetic Resonance Imaging-Ultrasound Fusion Targeted Biopsy: A Systematic Review. *Eur Urol*, 2015. 68: 8.
<https://www.ncbi.nlm.nih.gov/pubmed/25454618>
157. Siddiqui, M.M., *et al.* Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA*, 2015. 313: 390.
<https://www.ncbi.nlm.nih.gov/pubmed/25626035>
158. Wegelin, O., *et al.* Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? *Eur Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27568655>
159. Panebianco, V., *et al.* Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. *Urol Oncol*, 2015. 33: 17 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/25443268>
160. Baco, E., *et al.* A Randomized Controlled Trial To Assess and Compare the Outcomes of Two-core Prostate Biopsy Guided by Fused Magnetic Resonance and Transrectal Ultrasound Images and Traditional 12-core Systematic Biopsy. *Eur Urol*, 2016. 69: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/25862143>

161. Tonttila, P.P., *et al.* Prebiopsy Multiparametric Magnetic Resonance Imaging for Prostate Cancer Diagnosis in Biopsy-naive Men with Suspected Prostate Cancer Based on Elevated Prostate-specific Antigen Values: Results from a Randomized Prospective Blinded Controlled Trial. *Eur Urol*, 2016. 69: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/26033153>
162. Puech, P., *et al.* Prostate cancer diagnosis: multiparametric MR-targeted biopsy with cognitive and transrectal US-MR fusion guidance versus systematic biopsy--prospective multicenter study. *Radiology*, 2013. 268: 461.
<https://www.ncbi.nlm.nih.gov/pubmed/23579051>
163. Wysock, J.S., *et al.* A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. *Eur Urol*, 2014. 66: 343.
<https://www.ncbi.nlm.nih.gov/pubmed/24262102>
164. Arsov, C., *et al.* Prospective randomized trial comparing magnetic resonance imaging (MRI)-guided in-bore biopsy to MRI-ultrasound fusion and transrectal ultrasound-guided prostate biopsy in patients with prior negative biopsies. *Eur Urol*, 2015. 68: 713.
<https://www.ncbi.nlm.nih.gov/pubmed/26116294>
165. Hansen, N.L., *et al.* The influence of prostate-specific antigen density on positive and negative predictive values of multiparametric magnetic resonance imaging to detect Gleason score 7-10 prostate cancer in a repeat biopsy setting. *BJU Int*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27488931>
166. Weinreb, J.C., *et al.* PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. *Eur Urol*, 2016. 69: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/26427566>
167. Mertan, F.V., *et al.* Prospective Evaluation of the Prostate Imaging Reporting and Data System Version 2 for Prostate Cancer Detection. *J Urol*, 2016. 196: 690.
<https://www.ncbi.nlm.nih.gov/pubmed/27101772>
168. Rosenkrantz, A.B., *et al.* Interobserver Reproducibility of the PI-RADS Version 2 Lexicon: A Multicenter Study of Six Experienced Prostate Radiologists. *Radiology*, 2016. 280: 793.
<https://www.ncbi.nlm.nih.gov/pubmed/27035179>
169. Muller, B.G., *et al.* Prostate Cancer: Interobserver Agreement and Accuracy with the Revised Prostate Imaging Reporting and Data System at Multiparametric MR Imaging. *Radiology*, 2015. 277: 741.
<https://www.ncbi.nlm.nih.gov/pubmed/26098458>
170. Zhao, C., *et al.* The efficiency of multiparametric magnetic resonance imaging (mpMRI) using PI-RADS Version 2 in the diagnosis of clinically significant prostate cancer. *Clin Imaging*, 2016. 40: 885.
<https://www.ncbi.nlm.nih.gov/pubmed/27179959>
171. Kasel-Seibert, M., *et al.* Assessment of PI-RADS v2 for the Detection of Prostate Cancer. *Eur J Radiol*, 2016. 85: 726.
<https://www.ncbi.nlm.nih.gov/pubmed/26971415>
172. Niaf, E., *et al.* Prostate focal peripheral zone lesions: characterization at multiparametric MR imaging--influence of a computer-aided diagnosis system. *Radiology*, 2014. 271: 761.
<https://www.ncbi.nlm.nih.gov/pubmed/24592959>
173. Litjens, G.J., *et al.* Clinical evaluation of a computer-aided diagnosis system for determining cancer aggressiveness in prostate MRI. *Eur Radiol*, 2015. 25: 3187.
<https://www.ncbi.nlm.nih.gov/pubmed/26060063>
174. Hoang Dinh, A., *et al.* Quantitative Analysis of Prostate Multiparametric MR Images for Detection of Aggressive Prostate Cancer in the Peripheral Zone: A Multiple Imager Study. *Radiology*, 2016. 280: 117.
<https://www.ncbi.nlm.nih.gov/pubmed/26859255>
175. Iczkowski, K.A., *et al.* Needle core length in sextant biopsy influences prostate cancer detection rate. *Urology*, 2002. 59: 698.
<https://www.ncbi.nlm.nih.gov/pubmed/11992843>
176. Van der Kwast, T., *et al.* Guidelines on processing and reporting of prostate biopsies: the 2013 update of the pathology committee of the European Randomized Study of Screening for Prostate Cancer (ERSPC). *Virchows Arch*, 2013. 463: 367.
<https://www.ncbi.nlm.nih.gov/pubmed/23918245>

177. Rogatsch, H., *et al.* Diagnostic effect of an improved preembedding method of prostate needle biopsy specimens. *Hum Pathol*, 2000. 31: 1102.
<https://www.ncbi.nlm.nih.gov/pubmed/11014578>
178. Novis, D.A., *et al.* Diagnostic uncertainty expressed in prostate needle biopsies. A College of American Pathologists Q-probes Study of 15,753 prostate needle biopsies in 332 institutions. *Arch Pathol Lab Med*, 1999. 123: 687.
<https://www.ncbi.nlm.nih.gov/pubmed/10420224>
179. Iczkowski, K.A. Current prostate biopsy interpretation: criteria for cancer, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, and use of immunostains. *Arch Pathol Lab Med*, 2006. 130: 835.
<https://www.ncbi.nlm.nih.gov/pubmed/16740037>
180. Reyes, A.O., *et al.* Diagnostic effect of complete histologic sampling of prostate needle biopsy specimens. *Am J Clin Pathol*, 1998. 109: 416.
<https://www.ncbi.nlm.nih.gov/pubmed/9535395>
181. Epstein, J.I., *et al.* The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol*, 2016. 40: 244.
<https://www.ncbi.nlm.nih.gov/pubmed/26492179>
182. Kweldam, C.F., *et al.* Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. *Mod Pathol*, 2016. 29: 630.
<https://www.ncbi.nlm.nih.gov/pubmed/26939875>
183. Sebo, T.J., *et al.* Predicting prostate carcinoma volume and stage at radical prostatectomy by assessing needle biopsy specimens for percent surface area and cores positive for carcinoma, perineural invasion, Gleason score, DNA ploidy and proliferation, and preoperative serum prostate specific antigen: a report of 454 cases. *Cancer*, 2001. 91: 2196.
<https://www.ncbi.nlm.nih.gov/pubmed/11391602>
184. Grossklaus, D.J., *et al.* Percent of cancer in the biopsy set predicts pathological findings after prostatectomy. *J Urol*, 2002. 167: 2032.
<https://www.ncbi.nlm.nih.gov/pubmed/11956432>
185. Freedland, S.J., *et al.* Preoperative model for predicting prostate specific antigen recurrence after radical prostatectomy using percent of biopsy tissue with cancer, biopsy Gleason grade and serum prostate specific antigen. *J Urol*, 2004. 171: 2215.
<https://www.ncbi.nlm.nih.gov/pubmed/15126788>
186. Brimo, F., *et al.* Prognostic value of various morphometric measurements of tumour extent in prostate needle core tissue. *Histopathology*, 2008. 53: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/18752501>
187. Bangma, C.H., *et al.* Active surveillance for low-risk prostate cancer. *Crit Rev Oncol Hematol*, 2013. 85: 295.
<https://www.ncbi.nlm.nih.gov/pubmed/22878262>
188. Shore, N., *et al.* Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. *Curr Med Res Opin*, 2014. 30: 547.
<https://www.ncbi.nlm.nih.gov/pubmed/24320750>
189. Sehdev, A.E., *et al.* Comparative analysis of sampling methods for grossing radical prostatectomy specimens performed for nonpalpable (stage T1c) prostatic adenocarcinoma. *Hum Pathol*, 2001. 32: 494.
<https://www.ncbi.nlm.nih.gov/pubmed/11381367>
190. Ruijter, E.T., *et al.* Rapid microwave-stimulated fixation of entire prostatectomy specimens. Biomed-II MPC Study Group. *J Pathol*, 1997. 183: 369.
<https://www.ncbi.nlm.nih.gov/pubmed/9422995>
191. Chan, N.G., *et al.* Pathological reporting of colorectal cancer specimens: a retrospective survey in an academic Canadian pathology department. *Can J Surg*, 2008. 51: 284.
<https://www.ncbi.nlm.nih.gov/pubmed/18815652>
192. Partin, A.W., *et al.* Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology*, 2001. 58: 843.
<https://www.ncbi.nlm.nih.gov/pubmed/11744442>
193. Harnden, P., *et al.* Should the Gleason grading system for prostate cancer be modified to account for high-grade tertiary components? A systematic review and meta-analysis. *Lancet Oncol*, 2007. 8: 411.
<https://www.ncbi.nlm.nih.gov/pubmed/17466898>

194. Magi-Galluzzi, C., *et al.* International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. *Mod Pathol*, 2011. 24: 26.
<https://www.ncbi.nlm.nih.gov/pubmed/20802467>
195. Epstein, J.I., *et al.* Influence of capsular penetration on progression following radical prostatectomy: a study of 196 cases with long-term followup. *J Urol*, 1993. 150: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/7685422>
196. Marks, R.A., *et al.* The relationship between the extent of surgical margin positivity and prostate specific antigen recurrence in radical prostatectomy specimens. *Hum Pathol*, 2007. 38: 1207.
<https://www.ncbi.nlm.nih.gov/pubmed/17490720>
197. Sung, M.T., *et al.* Radial distance of extraprostatic extension measured by ocular micrometer is an independent predictor of prostate-specific antigen recurrence: A new proposal for the substaging of pT3a prostate cancer. *Am J Surg Pathol*, 2007. 31: 311.
<https://www.ncbi.nlm.nih.gov/pubmed/17255778>
198. Aydin, H., *et al.* Positive proximal (bladder neck) margin at radical prostatectomy confers greater risk of biochemical progression. *Urology*, 2004. 64: 551.
<https://www.ncbi.nlm.nih.gov/pubmed/15351591>
199. Ploussard, G., *et al.* The prognostic significance of bladder neck invasion in prostate cancer: is microscopic involvement truly a T4 disease? *BJU Int*, 2010. 105: 776.
<https://www.ncbi.nlm.nih.gov/pubmed/19863529>
200. Hoedemaeker, R.F., *et al.* Staging prostate cancer. *Microsc Res Tech*, 2000. 51: 423.
<https://www.ncbi.nlm.nih.gov/pubmed/11074612>
201. Stamey, T.A., *et al.* Prostate cancer is highly predictable: a prognostic equation based on all morphological variables in radical prostatectomy specimens. *J Urol*, 2000. 163: 1155.
<https://www.ncbi.nlm.nih.gov/pubmed/10737486>
202. Epstein, J.I., *et al.* Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. *Scand J Urol Nephrol Suppl*, 2005: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/16019758>
203. Kikuchi, E., *et al.* Is tumor volume an independent prognostic factor in clinically localized prostate cancer? *J Urol*, 2004. 172: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/15247716>
204. van Oort, I.M., *et al.* Maximum tumor diameter is not an independent prognostic factor in high-risk localized prostate cancer. *World J Urol*, 2008. 26: 237.
<https://www.ncbi.nlm.nih.gov/pubmed/18265988>
205. van der Kwast, T.H., *et al.* International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 2: T2 substaging and prostate cancer volume. *Mod Pathol*, 2011. 24: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/20818340>
206. Evans, A.J., *et al.* Interobserver variability between expert urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. *Am J Surg Pathol*, 2008. 32: 1503.
<https://www.ncbi.nlm.nih.gov/pubmed/18708939>
207. Chuang, A.Y., *et al.* Positive surgical margins in areas of capsular incision in otherwise organ-confined disease at radical prostatectomy: histologic features and pitfalls. *Am J Surg Pathol*, 2008. 32: 1201.
<https://www.ncbi.nlm.nih.gov/pubmed/18580493>
208. Sammon, J.D., *et al.* Risk factors for biochemical recurrence following radical perineal prostatectomy in a large contemporary series: a detailed assessment of margin extent and location. *Urol Oncol*, 2013. 31: 1470.
<https://www.ncbi.nlm.nih.gov/pubmed/22534086>
209. Spigelman, S.S., *et al.* Rectal examination in volume determination of carcinoma of the prostate: clinical and anatomical correlations. *J Urol*, 1986. 136: 1228.
<https://www.ncbi.nlm.nih.gov/pubmed/3773095>
210. Partin, A.W., *et al.* Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. *J Urol*, 1990. 143: 747.
<https://www.ncbi.nlm.nih.gov/pubmed/1690309>
211. Freedland, S.J., *et al.* Percent prostate needle biopsy tissue with cancer is more predictive of biochemical failure or adverse pathology after radical prostatectomy than prostate specific antigen or Gleason score. *J Urol*, 2002. 167: 516.
<https://www.ncbi.nlm.nih.gov/pubmed/11792909>

212. Quinn, D.I., *et al.* Prognostic significance of preoperative factors in localized prostate carcinoma treated with radical prostatectomy: importance of percentage of biopsies that contain tumor and the presence of biopsy perineural invasion. *Cancer*, 2003. 97: 1884.
<https://www.ncbi.nlm.nih.gov/pubmed/12673714>
213. Eifler, J.B., *et al.* An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. *BJU Int*, 2013. 111: 22.
<https://www.ncbi.nlm.nih.gov/pubmed/22834909>
214. Saliken, J.C., *et al.* Extraprostatic biopsy improves the staging of localized prostate cancer. *Can Assoc Radiol J*, 2000. 51: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/10786920>
215. Stone, N.N., *et al.* Indications for seminal vesicle biopsy and laparoscopic pelvic lymph node dissection in men with localized carcinoma of the prostate. *J Urol*, 1995. 154: 1392.
<https://www.ncbi.nlm.nih.gov/pubmed/7658545>
216. Allepuz Losa, C.A., *et al.* Seminal vesicle biopsy in prostate cancer staging. *J Urol*, 1995. 154: 1407.
<https://www.ncbi.nlm.nih.gov/pubmed/7544842>
217. Guillonneau, B., *et al.* Indications for preoperative seminal vesicle biopsies in staging of clinically localized prostatic cancer. *Eur Urol*, 1997. 32: 160.
<https://www.ncbi.nlm.nih.gov/pubmed/9286646>
218. Barqawi, A.B., *et al.* The role of 3-dimensional mapping biopsy in decision making for treatment of apparent early stage prostate cancer. *J Urol*, 2011. 186: 80.
<https://www.ncbi.nlm.nih.gov/pubmed/21571335>
219. Smith, J.A., Jr., *et al.* Transrectal ultrasound versus digital rectal examination for the staging of carcinoma of the prostate: results of a prospective, multi-institutional trial. *J Urol*, 1997. 157: 902.
<https://www.ncbi.nlm.nih.gov/pubmed/9072596>
220. Mitterberger, M., *et al.* The value of three-dimensional transrectal ultrasonography in staging prostate cancer. *BJU Int*, 2007. 100: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/17433033>
221. Sauvain, J.L., *et al.* Value of power doppler and 3D vascular sonography as a method for diagnosis and staging of prostate cancer. *Eur Urol*, 2003. 44: 21.
<https://www.ncbi.nlm.nih.gov/pubmed/12814671>
222. de Rooij, M., *et al.* Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. *Eur Urol*, 2016. 70: 233.
<https://www.ncbi.nlm.nih.gov/pubmed/26215604>
223. Jager, G.J., *et al.* Local staging of prostate cancer with endorectal MR imaging: correlation with histopathology. *AJR Am J Roentgenol*, 1996. 166: 845.
<https://www.ncbi.nlm.nih.gov/pubmed/8610561>
224. Cornud, F., *et al.* Extraprostatic spread of clinically localized prostate cancer: factors predictive of pT3 tumor and of positive endorectal MR imaging examination results. *Radiology*, 2002. 224: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/12091684>
225. Heijmink, S.W., *et al.* Prostate cancer: body-array versus endorectal coil MR imaging at 3 T--comparison of image quality, localization, and staging performance. *Radiology*, 2007. 244: 184.
<https://www.ncbi.nlm.nih.gov/pubmed/17495178>
226. Futterer, J.J., *et al.* Staging prostate cancer with dynamic contrast-enhanced endorectal MR imaging prior to radical prostatectomy: experienced versus less experienced readers. *Radiology*, 2005. 237: 541.
<https://www.ncbi.nlm.nih.gov/pubmed/16244263>
227. Wang, L., *et al.* Prostate cancer: incremental value of endorectal MR imaging findings for prediction of extracapsular extension. *Radiology*, 2004. 232: 133.
<https://www.ncbi.nlm.nih.gov/pubmed/15166321>
228. Poulakis, V., *et al.* Preoperative neural network using combined magnetic resonance imaging variables, prostate specific antigen and Gleason score to predict prostate cancer stage. *J Urol*, 2004. 172: 1306.
<https://www.ncbi.nlm.nih.gov/pubmed/15371829>
229. Schieda, N., *et al.* MRI assessment of pathological stage and surgical margins in anterior prostate cancer (APC) using subjective and quantitative analysis. *J Magn Reson Imaging*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27726247>
230. Lim, C., *et al.* Evaluation of apparent diffusion coefficient and MR volumetry as independent associative factors for extra-prostatic extension (EPE) in prostatic carcinoma. *J Magn Reson Imaging*, 2016. 43: 726.
<https://www.ncbi.nlm.nih.gov/pubmed/26303719>

231. Baco, E., *et al.* Predictive value of magnetic resonance imaging determined tumor contact length for extracapsular extension of prostate cancer. *J Urol*, 2015. 193: 466.
<https://www.ncbi.nlm.nih.gov/pubmed/25150643>
232. Raskolnikov, D., *et al.* The Role of Magnetic Resonance Image Guided Prostate Biopsy in Stratifying Men for Risk of Extracapsular Extension at Radical Prostatectomy. *J Urol*, 2015. 194: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/25623751>
233. D'Amico, A.V., *et al.* Endorectal magnetic resonance imaging as a predictor of biochemical outcome after radical prostatectomy in men with clinically localized prostate cancer. *J Urol*, 2000. 164: 759.
<https://www.ncbi.nlm.nih.gov/pubmed/10953141>
234. Engelbrecht, M.R., *et al.* Patient selection for magnetic resonance imaging of prostate cancer. *Eur Urol*, 2001. 40: 300.
<https://www.ncbi.nlm.nih.gov/pubmed/11684846>
235. Albert, J.M., *et al.* Magnetic resonance imaging-based treatment planning for prostate brachytherapy. *Brachytherapy*, 2013. 12: 30.
<https://www.ncbi.nlm.nih.gov/pubmed/22727474>
236. Stone, N.N., *et al.* Perineural invasion and seminal vesicle involvement predict pelvic lymph node metastasis in men with localized carcinoma of the prostate. *J Urol*, 1998. 160: 1722.
<https://www.ncbi.nlm.nih.gov/pubmed/9783940>
237. Pisansky, T.M., *et al.* Correlation of pretherapy prostate cancer characteristics with histologic findings from pelvic lymphadenectomy specimens. *Int J Radiat Oncol Biol Phys*, 1996. 34: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/12118563>
238. Cagiannos, I., *et al.* A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. *J Urol*, 2003. 170: 1798.
<https://www.ncbi.nlm.nih.gov/pubmed/14532779>
239. Abdollah, F., *et al.* Indications for pelvic nodal treatment in prostate cancer should change. Validation of the Roach formula in a large extended nodal dissection series. *Int J Radiat Oncol Biol Phys*, 2012. 83: 624.
<https://www.ncbi.nlm.nih.gov/pubmed/22099031>
240. Haese, A., *et al.* Validation of a biopsy-based pathologic algorithm for predicting lymph node metastases in patients with clinically localized prostate carcinoma. *Cancer*, 2002. 95: 1016.
<https://www.ncbi.nlm.nih.gov/pubmed/12209685>
241. Abuzalouf, S., *et al.* Baseline staging of newly diagnosed prostate cancer: a summary of the literature. *J Urol*, 2004. 171: 2122.
<https://www.ncbi.nlm.nih.gov/pubmed/15126770>
242. Kiss, B., *et al.* Current Status of Lymph Node Imaging in Bladder and Prostate Cancer. *Urology*, 2016. 96: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/26966038>
243. Harisinghani, M.G., *et al.* Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med*, 2003. 348: 2491.
<https://www.ncbi.nlm.nih.gov/pubmed/12815134>
244. Hovels, A.M., *et al.* The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol*, 2008. 63: 387.
<https://www.ncbi.nlm.nih.gov/pubmed/18325358>
245. Flanigan, R.C., *et al.* Limited efficacy of preoperative computed tomographic scanning for the evaluation of lymph node metastasis in patients before radical prostatectomy. *Urology*, 1996. 48: 428.
<https://www.ncbi.nlm.nih.gov/pubmed/8804497>
246. Tiguert, R., *et al.* Lymph node size does not correlate with the presence of prostate cancer metastasis. *Urology*, 1999. 53: 367.
<https://www.ncbi.nlm.nih.gov/pubmed/9933056>
247. Spevack, L., *et al.* Predicting the patient at low risk for lymph node metastasis with localized prostate cancer: an analysis of four statistical models. *Int J Radiat Oncol Biol Phys*, 1996. 34: 543.
<https://www.ncbi.nlm.nih.gov/pubmed/8621276>
248. Thoeny, H.C., *et al.* Metastases in normal-sized pelvic lymph nodes: detection with diffusion-weighted MR imaging. *Radiology*, 2014. 273: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/24893049>
249. Brogsitter, C., *et al.* ¹⁸F-Choline, ¹¹C-choline and ¹¹C-acetate PET/CT: comparative analysis for imaging prostate cancer patients. *Eur J Nucl Med Mol Imaging*, 2013. 40 Suppl 1: S18.
<https://www.ncbi.nlm.nih.gov/pubmed/23579863>

250. Poulsen, M.H., *et al.* [¹⁸F]fluoromethylcholine (FCH) positron emission tomography/computed tomography (PET/CT) for lymph node staging of prostate cancer: a prospective study of 210 patients. *BJU Int*, 2012. 110: 1666.
<https://www.ncbi.nlm.nih.gov/pubmed/22520686>
251. von Eyben, F.E., *et al.* Meta-analysis of (11)C-choline and (18)F-choline PET/CT for management of patients with prostate cancer. *Nucl Med Commun*, 2014. 35: 221.
<https://www.ncbi.nlm.nih.gov/pubmed/24240194>
252. Van den Bergh, L., *et al.* Final analysis of a prospective trial on functional imaging for nodal staging in patients with prostate cancer at high risk for lymph node involvement. *Urol Oncol*, 2015. 33: 109 e23.
<https://www.ncbi.nlm.nih.gov/pubmed/25655681>
253. Pinaquy, J.B., *et al.* Comparative effectiveness of [(18) F]-fluorocholine PET-CT and pelvic MRI with diffusion-weighted imaging for staging in patients with high-risk prostate cancer. *Prostate*, 2015. 75: 323.
<https://www.ncbi.nlm.nih.gov/pubmed/25393215>
254. Heck, M.M., *et al.* Prospective comparison of computed tomography, diffusion-weighted magnetic resonance imaging and [¹¹C]choline positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer patients. *Eur J Nucl Med Mol Imaging*, 2014. 41: 694.
<https://www.ncbi.nlm.nih.gov/pubmed/24297503>
255. Budiharto, T., *et al.* Prospective evaluation of ¹¹C-choline positron emission tomography/computed tomography and diffusion-weighted magnetic resonance imaging for the nodal staging of prostate cancer with a high risk of lymph node metastases. *Eur Urol*, 2011. 60: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/21292388>
256. Perera, M., *et al.* Sensitivity, Specificity, and Predictors of Positive ⁶⁸Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27363387>
257. Shen, G., *et al.* Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. *Skeletal Radiol*, 2014. 43: 1503.
<https://www.ncbi.nlm.nih.gov/pubmed/24841276>
258. Even-Sapir, E., *et al.* The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, ¹⁸F-fluoride PET, and ¹⁸F-fluoride PET/CT. *J Nucl Med*, 2006. 47: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/16455635>
259. Briganti, A., *et al.* When to perform bone scan in patients with newly diagnosed prostate cancer: external validation of the currently available guidelines and proposal of a novel risk stratification tool. *Eur Urol*, 2010. 57: 551.
<https://www.ncbi.nlm.nih.gov/pubmed/20034730>
260. O'Sullivan, J.M., *et al.* Broadening the criteria for avoiding staging bone scans in prostate cancer: a retrospective study of patients at the Royal Marsden Hospital. *BJU Int*, 2003. 92: 685.
<https://www.ncbi.nlm.nih.gov/pubmed/14616446>
261. Ayyathurai, R., *et al.* A study on staging bone scans in newly diagnosed prostate cancer. *Urol Int*, 2006. 76: 209.
<https://www.ncbi.nlm.nih.gov/pubmed/16601380>
262. Tateishi, U., *et al.* A meta-analysis of (18)F-Fluoride positron emission tomography for assessment of metastatic bone tumor. *Ann Nucl Med*, 2010. 24: 523.
<https://www.ncbi.nlm.nih.gov/pubmed/20559896>
263. Evangelista, L., *et al.* Diagnostic imaging to detect and evaluate response to therapy in bone metastases from prostate cancer: current modalities and new horizons. *Eur J Nucl Med Mol Imaging*, 2016. 43: 1546.
<https://www.ncbi.nlm.nih.gov/pubmed/26956538>
264. Picchio, M., *et al.* [¹¹C]Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. *Eur J Nucl Med Mol Imaging*, 2012. 39: 13.
<https://www.ncbi.nlm.nih.gov/pubmed/21932120>

265. Gutzeit, A., *et al.* Comparison of diffusion-weighted whole body MRI and skeletal scintigraphy for the detection of bone metastases in patients with prostate or breast carcinoma. *Skeletal Radiol*, 2010. 39: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/20205350>
266. Lecouvet, F.E., *et al.* Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? *Eur Urol*, 2012. 62: 68.
<https://www.ncbi.nlm.nih.gov/pubmed/22366187>
267. Pasoglou, V., *et al.* One-step TNM staging of high-risk prostate cancer using magnetic resonance imaging (MRI): toward an upfront simplified "all-in-one" imaging approach? *Prostate*, 2014. 74: 469.
<https://www.ncbi.nlm.nih.gov/pubmed/24375774>
268. Eiber, M., *et al.* ⁶⁸Ga-labeled Prostate-specific Membrane Antigen Positron Emission Tomography for Prostate Cancer Imaging: The New Kid on the Block-Early or Too Early to Draw Conclusions? *Eur Urol*, 2016. 70: 938.
<https://www.ncbi.nlm.nih.gov/pubmed/27481174>
269. Albertsen, P.C. Observational studies and the natural history of screen-detected prostate cancer. *Curr Opin Urol*, 2015. 25: 232.
<https://www.ncbi.nlm.nih.gov/pubmed/25692723>
270. Welty, C.J., *et al.* Meaningful end points and outcomes in men on active surveillance for early-stage prostate cancer. *Curr Opin Urol*, 2014. 24: 288.
<https://www.ncbi.nlm.nih.gov/pubmed/24614347>
271. Hamdy, F.C., *et al.* 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*, 2016. 375: 1415.
<https://www.ncbi.nlm.nih.gov/pubmed/27626136>
272. Klotz, L., *et al.* Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*, 2015. 33: 272.
<https://www.ncbi.nlm.nih.gov/pubmed/25512465>
273. Yamamoto, T., *et al.* Metastatic Prostate Cancer in Men Initially Treated with Active Surveillance. *J Urol*, 2016. 195: 1409.
<https://www.ncbi.nlm.nih.gov/pubmed/26707510>
274. Thomsen, F.B., *et al.* Active surveillance for clinically localized prostate cancer--a systematic review. *J Surg Oncol*, 2014. 109: 830.
<https://www.ncbi.nlm.nih.gov/pubmed/24610744>
275. Loeb, S., *et al.* Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. *Eur Urol*, 2015. 67: 619.
<https://www.ncbi.nlm.nih.gov/pubmed/25457014>
276. Ha, Y.S., *et al.* Prostate-specific antigen density toward a better cutoff to identify better candidates for active surveillance. *Urology*, 2014. 84: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/24925834>
277. Montironi, R., *et al.* Consensus statement with recommendations on active surveillance inclusion criteria and definition of progression in men with localized prostate cancer: the critical role of the pathologist. *Virchows Arch*, 2014.
<https://www.ncbi.nlm.nih.gov/pubmed/25316188>
278. Moreira, D.M., *et al.* Baseline Perineural Invasion is Associated with Shorter Time to Progression in Men with Prostate Cancer Undergoing Active Surveillance: Results from the REDEEM Study. *J Urol*, 2015. 194: 1258.
<https://www.ncbi.nlm.nih.gov/pubmed/25988518>
279. Musunuru, H.B., *et al.* Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience. *J Urol*, 2016. 196: 1651.
<https://www.ncbi.nlm.nih.gov/pubmed/27569437>
280. Raldow, A.C., *et al.* Risk Group and Death From Prostate Cancer: Implications for Active Surveillance in Men With Favorable Intermediate-Risk Prostate Cancer. *JAMA Oncol*, 2015. 1: 334.
<https://www.ncbi.nlm.nih.gov/pubmed/26181182>
281. Morash, C., *et al.* Active surveillance for the management of localized prostate cancer: Guideline recommendations. *Can Urol Assoc J*, 2015. 9: 171.
<https://www.ncbi.nlm.nih.gov/pubmed/26225165>
282. Satasivam, P., *et al.* Can Confirmatory Biopsy be Omitted in Patients with Prostate Cancer Favorable Diagnostic Features on Active Surveillance? *J Urol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26192258>

283. Klein, E.A., *et al.* A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol*, 2014. 66: 550.
<https://www.ncbi.nlm.nih.gov/pubmed/24836057>
284. Berg, K.D., *et al.* ERG protein expression in diagnostic specimens is associated with increased risk of progression during active surveillance for prostate cancer. *Eur Urol*, 2014. 66: 851.
<https://www.ncbi.nlm.nih.gov/pubmed/24630684>
285. Cantiello, F., *et al.* PHI and PCA3 improve the prognostic performance of PRIAS and Epstein criteria in predicting insignificant prostate cancer in men eligible for active surveillance. *World J Urol*, 2016. 34: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/26194612>
286. Lawrentschuk, N., *et al.* 'Prostatic evasive anterior tumours': the role of magnetic resonance imaging. *BJU Int*, 2010. 105: 1231.
<https://www.ncbi.nlm.nih.gov/pubmed/19817743>
287. Schoots, I.G., *et al.* Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. *Eur Urol*, 2015. 67: 627.
<https://www.ncbi.nlm.nih.gov/pubmed/25511988>
288. Recabal, P., *et al.* The Efficacy of Multiparametric Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Risk Classification for Patients with Prostate Cancer on Active Surveillance. *J Urol*, 2016. 196: 374.
<https://www.ncbi.nlm.nih.gov/pubmed/26920465>
289. Pessoa, R.R., *et al.* Value of 3-Tesla multiparametric magnetic resonance imaging and targeted biopsy for improved risk stratification in patients considered for active surveillance. *BJU Int*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27500389>
290. Kamrava, M., *et al.* Multiparametric magnetic resonance imaging for prostate cancer improves Gleason score assessment in favorable risk prostate cancer. *Pract Radiat Oncol*, 2015. 5: 411.
<https://www.ncbi.nlm.nih.gov/pubmed/26059510>
291. Ouzzane, A., *et al.* Magnetic Resonance Imaging Targeted Biopsy Improves Selection of Patients Considered for Active Surveillance for Clinically Low Risk Prostate Cancer Based on Systematic Biopsies. *J Urol*, 2015. 194: 350.
<https://www.ncbi.nlm.nih.gov/pubmed/25747105>
292. Da Rosa, M.R., *et al.* A prospective comparison of MRI-US fused targeted biopsy versus systematic ultrasound-guided biopsy for detecting clinically significant prostate cancer in patients on active surveillance. *J Magn Reson Imaging*, 2015. 41: 220.
<https://www.ncbi.nlm.nih.gov/pubmed/25044935>
293. Ma, T.M., *et al.* The Role of Multiparametric Magnetic Resonance Imaging/Ultrasound Fusion Biopsy in Active Surveillance. *Eur Urol*, 2017. 71: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/27236496>
294. Abdi, H., *et al.* Multiparametric magnetic resonance imaging enhances detection of significant tumor in patients on active surveillance for prostate cancer. *Urology*, 2015. 85: 423.
<https://www.ncbi.nlm.nih.gov/pubmed/25623709>
295. Walton Diaz, A., *et al.* Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate cancer on active surveillance. *Urol Oncol*, 2015. 33: 202 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/25754621>
296. Felker, E.R., *et al.* Serial Magnetic Resonance Imaging in Active Surveillance of Prostate Cancer: Incremental Value. *J Urol*, 2016. 195: 1421.
<https://www.ncbi.nlm.nih.gov/pubmed/26674305>
297. Moore, C.M., *et al.* Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer: The PRECISE Recommendations-A Report of a European School of Oncology Task Force. *Eur Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27349615>
298. Satasivam, P., *et al.* Can Confirmatory Biopsy be Omitted in Patients with Prostate Cancer Favorable Diagnostic Features on Active Surveillance? *J Urol*, 2016. 195: 74.
<https://www.ncbi.nlm.nih.gov/pubmed/26192258>
299. Nassiri, N., *et al.* Targeted Biopsy to Detect Gleason Score Upgrading during Active Surveillance for Men with Low versus Intermediate Risk Prostate Cancer. *J Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27639713>
300. Ross, A.E., *et al.* Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. *J Clin Oncol*, 2010. 28: 2810.
<https://www.ncbi.nlm.nih.gov/pubmed/20439642>

301. Thomsen, F.B., *et al.* Association between PSA kinetics and cancer-specific mortality in patients with localised prostate cancer: analysis of the placebo arm of the SPCG-6 study. *Ann Oncol*, 2016. 27: 460.
<https://www.ncbi.nlm.nih.gov/pubmed/26681677>
302. Klotz, L., *et al.* Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol*, 2010. 28: 126.
<https://www.ncbi.nlm.nih.gov/pubmed/19917860>
303. Bellardita, L., *et al.* How does active surveillance for prostate cancer affect quality of life? A systematic review. *Eur Urol*, 2015. 67: 637.
<https://www.ncbi.nlm.nih.gov/pubmed/25454617>
304. van As, N.J., *et al.* Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. *Eur Urol*, 2008. 54: 1297.
<https://www.ncbi.nlm.nih.gov/pubmed/18342430>
305. Carter, H.B., *et al.* Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. *J Urol*, 2007. 178: 2359.
<https://www.ncbi.nlm.nih.gov/pubmed/17936806>
306. Adamy, A., *et al.* Role of prostate specific antigen and immediate confirmatory biopsy in predicting progression during active surveillance for low risk prostate cancer. *J Urol*, 2011. 185: 477.
<https://www.ncbi.nlm.nih.gov/pubmed/21167529>
307. Soloway, M.S., *et al.* Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. *Eur Urol*, 2010. 58: 831.
<https://www.ncbi.nlm.nih.gov/pubmed/20800964>
308. Roemeling, S., *et al.* Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. *Eur Urol*, 2007. 51: 1244.
<https://www.ncbi.nlm.nih.gov/pubmed/17161520>
309. Khatami, A., *et al.* PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. *Int J Cancer*, 2007. 120: 170.
<https://www.ncbi.nlm.nih.gov/pubmed/17013897>
310. Adolfsson, J. Watchful waiting and active surveillance: the current position. *BJU Int*, 2008. 102: 10.
<https://www.ncbi.nlm.nih.gov/pubmed/18422774>
311. Chodak, G.W., *et al.* Results of conservative management of clinically localized prostate cancer. *N Engl J Med*, 1994. 330: 242.
<https://www.ncbi.nlm.nih.gov/pubmed/8272085>
312. Sandblom, G., *et al.* Long-term survival in a Swedish population-based cohort of men with prostate cancer. *Urology*, 2000. 56: 442.
<https://www.ncbi.nlm.nih.gov/pubmed/10962312>
313. Johansson, J.E., *et al.* Natural history of localised prostatic cancer. A population-based study in 223 untreated patients. *Lancet*, 1989. 1: 799.
<https://www.ncbi.nlm.nih.gov/pubmed/2564901>
314. Bill-Axelson, A., *et al.* Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*, 2005. 352: 1977.
<https://www.ncbi.nlm.nih.gov/pubmed/15888698>
315. Adolfsson, J., *et al.* The 20-Yr outcome in patients with well- or moderately differentiated clinically localized prostate cancer diagnosed in the pre-PSA era: the prognostic value of tumour ploidy and comorbidity. *Eur Urol*, 2007. 52: 1028.
<https://www.ncbi.nlm.nih.gov/pubmed/>
316. Jonsson, E., *et al.* Adenocarcinoma of the prostate in Iceland: a population-based study of stage, Gleason grade, treatment and long-term survival in males diagnosed between 1983 and 1987. *Scand J Urol Nephrol*, 2006. 40: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/16916765>
317. Lu-Yao, G.L., *et al.* Outcomes of localized prostate cancer following conservative management. *Jama*, 2009. 302: 1202.
<https://www.ncbi.nlm.nih.gov/pubmed/19755699>
318. Hayes, J.H., *et al.* Observation versus initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis. *Ann Intern Med*, 2013. 158: 853.
<https://www.ncbi.nlm.nih.gov/pubmed/23778902>
319. Albertsen, P.C., *et al.* Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *Jama*, 1998. 280: 975.
<https://www.ncbi.nlm.nih.gov/pubmed/9749479>

320. Albertsen, P.C., *et al.* Statistical considerations when assessing outcomes following treatment for prostate cancer. *J Urol*, 1999. 162: 439.
<https://www.ncbi.nlm.nih.gov/pubmed/10411053>
321. Iversen, P., *et al.* Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. *J Urol*, 2004. 172: 1871.
<https://www.ncbi.nlm.nih.gov/pubmed/15540741>
322. Albertsen, P.C., *et al.* Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol*, 2011. 29: 1335.
<https://www.ncbi.nlm.nih.gov/pubmed/21357791>
323. Bill-Axelson, A., *et al.* Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*, 2011. 364: 1708.
<https://www.ncbi.nlm.nih.gov/pubmed/21542742>
324. Wilt, T.J., *et al.* Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*, 2012. 367: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/22808955>
325. Steineck, G., *et al.* Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med*, 2002. 347: 790.
<https://www.ncbi.nlm.nih.gov/pubmed/12226149>
326. Jacobs, B.L., *et al.* Use of advanced treatment technologies among men at low risk of dying from prostate cancer. *Jama*, 2013. 309: 2587.
<https://www.ncbi.nlm.nih.gov/pubmed/23800935>
327. Loeb, S., *et al.* Population based study of use and determinants of active surveillance and watchful waiting for low and intermediate risk prostate cancer. *J Urol*, 2013. 190: 1742.
<https://www.ncbi.nlm.nih.gov/pubmed/23727309>
328. Studer, U.E., *et al.* Using PSA to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (EORTC 30891). *Eur Urol*, 2008. 53: 941.
<https://www.ncbi.nlm.nih.gov/pubmed/18191322>
329. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. *Br J Urol*, 1997. 79: 235.
<https://www.ncbi.nlm.nih.gov/pubmed/9052476>
330. Walsh, P.C. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. *J Urol*, 1997. 158: 1623.
<https://www.ncbi.nlm.nih.gov/pubmed/9302187>
331. Bianco, F.J., Jr., *et al.* Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). *Urology*, 2005. 66: 83.
<https://www.ncbi.nlm.nih.gov/pubmed/16194712>
332. Walz, J., *et al.* A nomogram predicting 10-year life expectancy in candidates for radical prostatectomy or radiotherapy for prostate cancer. *J Clin Oncol*, 2007. 25: 3576.
<https://www.ncbi.nlm.nih.gov/pubmed/17704404>
333. Bill-Axelson, A., *et al.* Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med*, 2014. 370: 932.
<https://www.ncbi.nlm.nih.gov/pubmed/24597866>
334. Yaxley, J.W., *et al.* Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet*, 2016. 388: 1057.
<https://www.ncbi.nlm.nih.gov/pubmed/27474375>
335. Allan, C., *et al.* Laparoscopic versus Robotic-Assisted Radical Prostatectomy for the Treatment of Localised Prostate Cancer: A Systematic Review. *Urol Int*, 2016. 96: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/26201500>
336. Eastham, J.A., *et al.* Variations among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. *J Urol*, 2003. 170: 2292.
<https://www.ncbi.nlm.nih.gov/pubmed/14634399>
337. Vickers, A.J., *et al.* The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. *Lancet Oncol*, 2009. 10: 475.
<https://www.ncbi.nlm.nih.gov/pubmed/19342300>

338. Trinh, Q.D., *et al.* A systematic review of the volume-outcome relationship for radical prostatectomy. *Eur Urol*, 2013. 64: 786.
<https://www.ncbi.nlm.nih.gov/pubmed/23664423>
339. Kattan, M.W., *et al.* Algorithms for prostate-specific antigen recurrence after treatment of localized prostate cancer. *Clin Prostate Cancer*, 2003 15040880. 1: 221.
<https://www.ncbi.nlm.nih.gov/pubmed/15040880>
340. Briganti, A., *et al.* Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. *Eur Urol*, 2012. 61: 480.
<https://www.ncbi.nlm.nih.gov/pubmed/22078338>
341. Rider, J.R., *et al.* Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. *Eur Urol*, 2013. 63: 88.
<https://www.ncbi.nlm.nih.gov/pubmed/22902040>
342. Yossepowitch, O., *et al.* Radical prostatectomy for clinically localized, high risk prostate cancer: critical analysis of risk assessment methods. *J Urol*, 2007. 178: 493.
<https://www.ncbi.nlm.nih.gov/pubmed/17561152>
343. Donohue, J.F., *et al.* Poorly differentiated prostate cancer treated with radical prostatectomy: long-term outcome and incidence of pathological downgrading. *J Urol*, 2006. 176: 991.
<https://www.ncbi.nlm.nih.gov/pubmed/16890678>
344. Bastian, P.J., *et al.* Clinical and pathologic outcome after radical prostatectomy for prostate cancer patients with a preoperative Gleason sum of 8 to 10. *Cancer*, 2006. 107: 1265.
<https://www.ncbi.nlm.nih.gov/pubmed/16900523>
345. Yossepowitch, O., *et al.* Secondary therapy, metastatic progression, and cancer-specific mortality in men with clinically high-risk prostate cancer treated with radical prostatectomy. *Eur Urol*, 2008. 53: 950.
<https://www.ncbi.nlm.nih.gov/pubmed/17950521>
346. Walz, J., *et al.* Pathological results and rates of treatment failure in high-risk prostate cancer patients after radical prostatectomy. *BJU Int*, 2011. 107: 765.
<https://www.ncbi.nlm.nih.gov/pubmed/20875089>
347. Chang, K., *et al.* Comparison of two adjuvant hormone therapy regimens in patients with high-risk localized prostate cancer after radical prostatectomy: primary results of study CU1005. *Asian J Androl*, 2016. 18: 452.
<https://www.ncbi.nlm.nih.gov/pubmed/26323560>
348. D'Amico, A.V., *et al.* Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol*, 1999. 17: 168.
<https://www.ncbi.nlm.nih.gov/pubmed/10458230>
349. Spahn, M., *et al.* Outcome predictors of radical prostatectomy in patients with prostate-specific antigen greater than 20 ng/ml: a European multi-institutional study of 712 patients. *Eur Urol*, 2010. 58: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/20299147>
350. Zwergel, U., *et al.* Outcome of prostate cancer patients with initial PSA > or =20 ng/ml undergoing radical prostatectomy. *Eur Urol*, 2007. 52: 1058.
<https://www.ncbi.nlm.nih.gov/pubmed/17418938>
351. Magheli, A., *et al.* Importance of tumor location in patients with high preoperative prostate specific antigen levels (greater than 20 ng/ml) treated with radical prostatectomy. *J Urol*, 2007. 178: 1311.
<https://www.ncbi.nlm.nih.gov/pubmed/17698095>
352. Gerber, G.S., *et al.* Results of radical prostatectomy in men with locally advanced prostate cancer: multi-institutional pooled analysis. *Eur Urol*, 1997. 32: 385.
<https://www.ncbi.nlm.nih.gov/pubmed/9412793>
353. Ward, J.F., *et al.* Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int*, 2005. 95: 751.
<https://www.ncbi.nlm.nih.gov/pubmed/15794776>
354. Hsu, C.Y., *et al.* Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. *Eur Urol*, 2007. 51: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/16797831>
355. Joniau, S., *et al.* Pretreatment tables predicting pathologic stage of locally advanced prostate cancer. *Eur Urol*, 2015. 67: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/24684960>

356. Loeb, S., *et al.* Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. *Urology*, 2007. 69: 1170. <https://www.ncbi.nlm.nih.gov/pubmed/17572209>
357. Carver, B.S., *et al.* Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. *J Urol*, 2006. 176: 564. <https://www.ncbi.nlm.nih.gov/pubmed/16813890>
358. Freedland, S.J., *et al.* Radical prostatectomy for clinical stage T3a disease. *Cancer*, 2007. 109: 1273. <https://www.ncbi.nlm.nih.gov/pubmed/17315165>
359. Xylinas, E., *et al.* Oncological control after radical prostatectomy in men with clinical T3 prostate cancer: a single-centre experience. *BJU Int*, 2009. 103: 1173. <https://www.ncbi.nlm.nih.gov/pubmed/19040530>
360. Joniau, S., *et al.* Radical prostatectomy in very high-risk localized prostate cancer: long-term outcomes and outcome predictors. *Scand J Urol Nephrol*, 2012. 46: 164. <https://www.ncbi.nlm.nih.gov/pubmed/22364377>
361. Johnstone, P.A., *et al.* Radical prostatectomy for clinical T4 prostate cancer. *Cancer*, 2006. 106: 2603. <https://www.ncbi.nlm.nih.gov/pubmed/16700037>
362. Moltzahn, F., *et al.* Predicting prostate cancer-specific outcome after radical prostatectomy among men with very high-risk cT3b/4 PCa: a multi-institutional outcome study of 266 patients. *Prostate Cancer Prostatic Dis*, 2015. 18: 31. <https://www.ncbi.nlm.nih.gov/pubmed/25535100>
363. Moschini, M., *et al.* Outcomes for Patients with Clinical Lymphadenopathy Treated with Radical Prostatectomy. *Eur Urol*, 2015. <https://www.ncbi.nlm.nih.gov/pubmed/26264160>
364. Dell'Oglio, P., *et al.* External validation of the European association of urology recommendations for pelvic lymph node dissection in patients treated with robot-assisted radical prostatectomy. *J Endourol*, 2014. 28: 416. <https://www.ncbi.nlm.nih.gov/pubmed/24188052>
365. Hinev, A.I., *et al.* Validation of nomograms predicting lymph node involvement in patients with prostate cancer undergoing extended pelvic lymph node dissection. *Urol Int*, 2014. 92: 300. <https://www.ncbi.nlm.nih.gov/pubmed/24480972>
366. Mattei, A., *et al.* The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. *Eur Urol*, 2008. 53: 118. <https://www.ncbi.nlm.nih.gov/pubmed/17709171>
367. Wit, E.M., *et al.* Sentinel Node Procedure in Prostate Cancer: A Systematic Review to Assess Diagnostic Accuracy. *Eur Urol*, 2016. Sep 14. pii: S0302-2838(16)30617-0. doi: 10.1016/j.eururo.2016.09.007. <https://www.ncbi.nlm.nih.gov/pubmed/27639533>
368. van der Poel, H.G., *et al.* Sentinel node biopsy for prostate cancer: report from a consensus panel meeting. *BJU Int*, 2017. <https://www.ncbi.nlm.nih.gov/pubmed/28188689>
369. Briganti, A., *et al.* Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. *Eur Urol*, 2009. 55: 261. <https://www.ncbi.nlm.nih.gov/pubmed/18838212>
370. Ghavamian, R., *et al.* Radical retropubic prostatectomy plus orchiectomy versus orchiectomy alone for pTxN+ prostate cancer: a matched comparison. *J Urol*, 1999. 161: 1223. <https://www.ncbi.nlm.nih.gov/pubmed/10081874>
371. Messing, E.M., *et al.* Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol*, 2006. 7: 472. <https://www.ncbi.nlm.nih.gov/pubmed/16750497>
372. Engel, J., *et al.* Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. *Eur Urol*, 2010. 57: 754. <https://www.ncbi.nlm.nih.gov/pubmed/20106588>
373. Steuber, T., *et al.* Radical prostatectomy improves progression-free and cancer-specific survival in men with lymph node positive prostate cancer in the prostate-specific antigen era: a confirmatory study. *BJU Int*, 2011. 107: 1755. <https://www.ncbi.nlm.nih.gov/pubmed/20942833>

374. Schumacher, M.C., *et al.* Good outcome for patients with few lymph node metastases after radical retropubic prostatectomy. *Eur Urol*, 2008. 54: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/18511183>
375. Abdollah, F., *et al.* Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol*, 2014. 32: 3939.
<https://www.ncbi.nlm.nih.gov/pubmed/25245445>
376. Rusthoven, C.G., *et al.* The impact of definitive local therapy for lymph node-positive prostate cancer: a population-based study. *Int J Radiat Oncol Biol Phys*, 2014. 88: 1064.
<https://www.ncbi.nlm.nih.gov/pubmed/24661660>
377. Abdollah, F., *et al.* More extensive pelvic lymph node dissection improves survival in patients with node-positive prostate cancer. *Eur Urol*, 2015. 67: 212.
<https://www.ncbi.nlm.nih.gov/pubmed/24882672>
378. Pound, C.R., *et al.* Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*, 1999. 281: 1591.
<https://www.ncbi.nlm.nih.gov/pubmed/10235151>
379. Aus, G., *et al.* Prognostic factors and survival in node-positive (N1) prostate cancer—a prospective study based on data from a Swedish population-based cohort. *Eur Urol*, 2003. 43: 627.
<https://www.ncbi.nlm.nih.gov/pubmed/12767363>
380. Cheng, L., *et al.* Risk of prostate carcinoma death in patients with lymph node metastasis. *Cancer*, 2001. 91: 66.
<https://www.ncbi.nlm.nih.gov/pubmed/11148561>
381. Seiler, R., *et al.* Removal of limited nodal disease in patients undergoing radical prostatectomy: long-term results confirm a chance for cure. *J Urol*, 2014. 191: 1280.
<https://www.ncbi.nlm.nih.gov/pubmed/24262495>
382. Bader, P., *et al.* Is a limited lymph node dissection an adequate staging procedure for prostate cancer? *J Urol*, 2002. 168: 514.
<https://www.ncbi.nlm.nih.gov/pubmed/12131300>
383. Passoni, N.M., *et al.* Prognosis of patients with pelvic lymph node (LN) metastasis after radical prostatectomy: value of extranodal extension and size of the largest LN metastasis. *BJU Int*, 2014. 114: 503.
<https://www.ncbi.nlm.nih.gov/pubmed/24053552>
384. Daneshmand, S., *et al.* Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. *J Urol*, 172: 2252.
[http://www.jurology.com/article/S0022-5347\(05\)61388-2/abstract](http://www.jurology.com/article/S0022-5347(05)61388-2/abstract)
385. Iversen, P., *et al.* Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. *BJU Int*, 2010. 105: 1074.
<https://www.ncbi.nlm.nih.gov/pubmed/22129214>
386. Kumar, S., *et al.* Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. *Cochrane Database Syst Rev*, 2006: CD006019.
<https://www.ncbi.nlm.nih.gov/pubmed/17054269>
387. Schweizer, M.T., *et al.* Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): important lessons for future trials. *Cancer*, 2013. 119: 3610.
<https://www.ncbi.nlm.nih.gov/pubmed/23943299>
388. Ramsay, C., *et al.* Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. *Health Technol Assess*, 2012. 16: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/23127367>
389. Montorsi, F., *et al.* Best practices in robot-assisted radical prostatectomy: recommendations of the Pasadena Consensus Panel. *Eur Urol*, 2012. 62: 368.
<https://www.ncbi.nlm.nih.gov/pubmed/22763081>
390. Novara, G., *et al.* Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. *Eur Urol*, 2012. 62: 382.
<https://www.ncbi.nlm.nih.gov/pubmed/22749851>
391. Novara, G., *et al.* Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. *Eur Urol*, 2012. 62: 431.
<https://www.ncbi.nlm.nih.gov/pubmed/22749853>

392. Ficarra, V., *et al.* Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. *Eur Urol*, 2012. 62: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/22749850>
393. Ficarra, V., *et al.* Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. *Eur Urol*, 2012. 62: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/22749852>
394. Haglind, E., *et al.* Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. *Eur Urol*, 2015. 68: 216.
<https://www.ncbi.nlm.nih.gov/pubmed/25770484>
395. Potosky, A.L., *et al.* Radical prostatectomy: does higher volume lead to better quality? *J Natl Cancer Inst*, 1999. 91: 1906.
<https://www.ncbi.nlm.nih.gov/pubmed/10564667>
396. Lepor, H., *et al.* Intraoperative and postoperative complications of radical retropubic prostatectomy in a consecutive series of 1,000 cases. *J Urol*, 2001. 166: 1729.
<https://www.ncbi.nlm.nih.gov/pubmed/11586211>
397. Augustin, H., *et al.* Intraoperative and perioperative morbidity of contemporary radical retropubic prostatectomy in a consecutive series of 1243 patients: results of a single center between 1999 and 2002. *Eur Urol*, 2003. 43: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/12565767>
398. Maffezzini, M., *et al.* Evaluation of complications and results in a contemporary series of 300 consecutive radical retropubic prostatectomies with the anatomic approach at a single institution. *Urology*, 2003. 61: 982.
<https://www.ncbi.nlm.nih.gov/pubmed/12736020>
399. Gontero, P., *et al.* Nerve-sparing radical retropubic prostatectomy: techniques and clinical considerations. *Prostate Cancer Prostatic Dis*, 2005. 8: 133.
<https://www.ncbi.nlm.nih.gov/pubmed/15711608>
400. Sokoloff, M.H., *et al.* Indications and contraindications for nerve-sparing radical prostatectomy. *Urol Clin North Am*, 2001. 28: 535.
<https://www.ncbi.nlm.nih.gov/pubmed/11590812>
401. Steuber, T., *et al.* Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. *J Urol*, 2006. 175: 939.
<https://www.ncbi.nlm.nih.gov/pubmed/16469587>
402. Zorn, K.C., *et al.* External validation of a nomogram for prediction of side-specific extracapsular extension at robotic radical prostatectomy. *J Endourol*, 2007. 21: 1345.
<https://www.ncbi.nlm.nih.gov/pubmed/18042028>
403. Beyer, B., *et al.* A feasible and time-efficient adaptation of NeuroSAFE for da Vinci robot-assisted radical prostatectomy. *Eur Urol*, 2014. 66: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/24411279>
404. Montorsi, F., *et al.* Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol*, 2008. 54: 924.
<https://www.ncbi.nlm.nih.gov/pubmed/18640769>
405. Pavlovich, C.P., *et al.* Nightly vs on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: results of a randomized double-blind trial with placebo. *BJU Int*, 2013. 112: 844.
<https://www.ncbi.nlm.nih.gov/pubmed/23937708>
406. Patel, H.R., *et al.* Effects of tadalafil treatment after bilateral nerve-sparing radical prostatectomy: quality of life, psychosocial outcomes, and treatment satisfaction results from a randomized, placebo-controlled phase IV study. *BMC Urol*, 2015. 15: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/25879460>
407. Dearnaley, D.P., *et al.* Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol*, 2014. 15: 464.
<https://www.ncbi.nlm.nih.gov/pubmed/24581940>
408. Martens, C., *et al.* Relationship of the International Prostate Symptom score with urinary flow studies, and catheterization rates following 125I prostate brachytherapy. *Brachytherapy*, 2006. 5: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/16563992>
409. Ling, C.C., *et al.* From IMRT to IGRT: frontierland or neverland? *Radiother Oncol*, 2006. 78: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/16413622>

410. Kuban, D.A., *et al.* Long-term failure patterns and survival in a randomized dose-escalation trial for prostate cancer. Who dies of disease? *Int J Radiat Oncol Biol Phys*, 2011. 79: 1310.
<https://www.ncbi.nlm.nih.gov/pubmed/20493642>
411. Zietman, A.L., *et al.* Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol*, 2010. 28: 1106.
<https://www.ncbi.nlm.nih.gov/pubmed/20124169>
412. Viani, G.A., *et al.* Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys*, 2009. 74: 1405.
<https://www.ncbi.nlm.nih.gov/pubmed/19616743>
413. Peeters, S.T., *et al.* Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol*, 2006. 24: 1990.
<https://www.ncbi.nlm.nih.gov/pubmed/16648499>
414. Beckendorf, V., *et al.* 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys*, 2011. 80: 1056.
<https://www.ncbi.nlm.nih.gov/pubmed/21147514>
415. Jones, C.U., *et al.* Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med*, 2011. 365: 107.
<https://www.ncbi.nlm.nih.gov/pubmed/21751904>
416. Bolla, M., *et al.* Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*, 2009. 360: 2516.
<https://www.ncbi.nlm.nih.gov/pubmed/19516032>
417. Fowler, J.F. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. *Acta Oncol*, 2005. 44: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/16076699>
418. Dasu, A., *et al.* Prostate alpha/beta revisited -- an analysis of clinical results from 14 168 patients. *Acta Oncol*, 2012. 51: 963.
<https://www.ncbi.nlm.nih.gov/pubmed/22966812>
419. Heemsbergen, W.D., *et al.* Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiother Oncol*, 2014. 110: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/24246414>
420. Kalbasi, A., *et al.* Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer. *JAMA Oncol*, 2015. 1: 897.
<https://www.ncbi.nlm.nih.gov/pubmed/26181727>
421. Zietman, A.L., *et al.* Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA*, 2005. 294: 1233.
<https://www.ncbi.nlm.nih.gov/pubmed/16160131>
422. Peeters, S.T., *et al.* Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys*, 2005. 61: 1019.
<https://www.ncbi.nlm.nih.gov/pubmed/15752881>
423. Dearnaley, D.P., *et al.* The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). *Radiother Oncol*, 2007. 83: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/17391791>
424. Kuban, D.A., *et al.* Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys*, 2008. 70: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/17765406>
425. Matzinger, O., *et al.* Acute toxicity of curative radiotherapy for intermediate- and high-risk localised prostate cancer in the EORTC trial 22991. *Eur J Cancer*, 2009. 45: 2825.
<https://www.ncbi.nlm.nih.gov/pubmed/19682889>
426. Zapatero, A., *et al.* Risk-Adapted Androgen Deprivation and Escalated Three-Dimensional Conformal Radiotherapy for Prostate Cancer: Does Radiation Dose Influence Outcome of Patients Treated With Adjuvant Androgen Deprivation? A GICOR Study. *J Clin Oncol*, 2005. 23: 6561.
<https://www.ncbi.nlm.nih.gov/pubmed/16170164>

427. Zelefsky, M.J., *et al.* Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol*, 2006. 176: 1415.
<https://www.ncbi.nlm.nih.gov/pubmed/16952647>
428. Vora, S.A., *et al.* Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*, 2007. 68: 1053.
<https://www.ncbi.nlm.nih.gov/pubmed/17398023>
429. Kupelian, P.A., *et al.* Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys*, 2007. 68: 1424.
<https://www.ncbi.nlm.nih.gov/pubmed/17544601>
430. Gomez-Iturriaga Pina, A., *et al.* Median 5 year follow-up of 125iodine brachytherapy as monotherapy in men aged <or=55 years with favorable prostate cancer. *Urology*, 2010. 75: 1412.
<https://www.ncbi.nlm.nih.gov/pubmed/20035986>
431. Ishiyama, H., *et al.* Genitourinary toxicity after high-dose-rate (HDR) brachytherapy combined with Hypofractionated External beam radiotherapy for localized prostate cancer: an analysis to determine the correlation between dose-volume histogram parameters in HDR brachytherapy and severity of toxicity. *Int J Radiat Oncol Biol Phys*, 2009. 75: 23.
<https://www.ncbi.nlm.nih.gov/pubmed/19243900>
432. Gelblum, D.Y., *et al.* Rectal complications associated with transperineal interstitial brachytherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*, 2000. 48: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/10924980>
433. Lee, W.R., *et al.* Late toxicity and biochemical recurrence after external-beam radiotherapy combined with permanent-source prostate brachytherapy. *Cancer*, 2007. 109: 1506.
<https://www.ncbi.nlm.nih.gov/pubmed/17340591>
434. Zelefsky, M.J., *et al.* Five-year biochemical outcome and toxicity with transperineal CT-planned permanent I-125 prostate implantation for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys*, 2000. 47: 1261.
<https://www.ncbi.nlm.nih.gov/pubmed/10889379>
435. Dearnaley, D., *et al.* Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol*, 2012. 13: 43.
<https://www.ncbi.nlm.nih.gov/pubmed/22169269>
436. Kuban, D.A., *et al.* Preliminary Report of a Randomized Dose Escalation Trial for Prostate Cancer using Hypofractionation. *Int J Radiat Oncol Biol Phys*, 78: S58.
[http://www.redjournal.org/article/S0360-3016\(10\)01144-2/abstract](http://www.redjournal.org/article/S0360-3016(10)01144-2/abstract)
437. Pollack, A., *et al.* Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol*, 2013. 31: 3860.
<https://www.ncbi.nlm.nih.gov/pubmed/24101042>
438. Aluwini, S., *et al.* Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. *Lancet Oncol*, 2015. 16: 274.
<https://www.ncbi.nlm.nih.gov/pubmed/25656287>
439. Lee, W.R., *et al.* Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. *J Clin Oncol*, 2016. 34: 2325.
<https://www.ncbi.nlm.nih.gov/pubmed/27044935440>
440. Dearnaley, D., *et al.* Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol*, 2016. 17: 1047.
[http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(16\)30102-4/abstract](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30102-4/abstract)
441. Hoffman, K.E., *et al.* Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. *Int J Radiat Oncol Biol Phys*, 2014. 88: 1074.
<https://www.ncbi.nlm.nih.gov/pubmed/24661661>
442. Pollack, A., *et al.* Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. *Int J Radiat Oncol Biol Phys*, 2006. 64: 518.
<https://www.ncbi.nlm.nih.gov/pubmed/16242256>

443. Aluwini, S., *et al.* Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. *Lancet Oncol*, 2016. 17: 464.
<https://www.ncbi.nlm.nih.gov/pubmed/26968359>
444. Incrocci, L., *et al.* Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*, 2016. 17: 1061.
<https://www.ncbi.nlm.nih.gov/pubmed/27339116>
445. Koontz, B.F., *et al.* A systematic review of hypofractionation for primary management of prostate cancer. *Eur Urol*, 2015. 68: 683.
<https://www.ncbi.nlm.nih.gov/pubmed/25171903>
446. Aluwini, S., *et al.* Stereotactic body radiotherapy with a focal boost to the MRI-visible tumor as monotherapy for low- and intermediate-risk prostate cancer: early results. *Radiat Oncol*, 2013. 8: 84.
<https://www.ncbi.nlm.nih.gov/pubmed/23570391>
447. Katz, A., *et al.* Stereotactic Body Radiation Therapy for Low-, Intermediate-, and High-Risk Prostate Cancer: Disease Control and Quality of Life at 6 Years. *Int J Radiat Oncol Biol Phys*, 2013. 87: S24.
[http://www.redjournal.org/article/S0360-3016\(13\)00738-4/abstract](http://www.redjournal.org/article/S0360-3016(13)00738-4/abstract)
448. Hocht, S., *et al.* Erratum to: Hypofractionated radiotherapy for localized prostate cancer. *Strahlenther Onkol*, 2016. 192: 830.
<https://www.ncbi.nlm.nih.gov/pubmed/27752707>
449. Freeman, D., *et al.* Multi-institutional registry for prostate cancer radiosurgery: a prospective observational clinical trial. *Front Oncol*, 2014. 4: 369.
<https://www.ncbi.nlm.nih.gov/pubmed/25657929>
450. Katz, A.J., *et al.* Quality of Life and Toxicity after SBRT for Organ-Confined Prostate Cancer, a 7-Year Study. *Front Oncol*, 2014. 4: 301.
<https://www.ncbi.nlm.nih.gov/pubmed/25389521>
451. Bolla, M., *et al.* External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*, 2010. 11: 1066.
<https://www.ncbi.nlm.nih.gov/pubmed/20933466452>
452. Pilepich, M.V., *et al.* Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys*, 2005. 61: 1285.
<https://www.ncbi.nlm.nih.gov/pubmed/15817329>
453. Roach, M., 3rd, *et al.* Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol*, 2008. 26: 585.
<https://www.ncbi.nlm.nih.gov/pubmed/18172188>
454. D'Amico, A.V., *et al.* Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA*, 2008. 299: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/18212313>
455. Denham, J.W., *et al.* Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol*, 2011. 12: 451.
<https://www.ncbi.nlm.nih.gov/pubmed/21440505>
456. Horwitz, E.M., *et al.* Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol*, 2008. 26: 2497.
<https://www.ncbi.nlm.nih.gov/pubmed/18413638>
457. Pisansky, T.M., *et al.* Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial 9910. *J Clin Oncol*, 2015. 33: 332.
<https://www.ncbi.nlm.nih.gov/pubmed/25534388>
458. Granfors, T., *et al.* Long-term followup of a randomized study of locally advanced prostate cancer treated with combined orchiectomy and external radiotherapy versus radiotherapy alone. *J Urol*, 2006. 176: 544.
<https://www.ncbi.nlm.nih.gov/pubmed/16813885>

459. Lawton, C.A., *et al.* An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys*, 2007. 69: 646.
<https://www.ncbi.nlm.nih.gov/pubmed/17531401>
460. Fossa, S.D., *et al.* Ten- and 15-year prostate cancer-specific survival in patients with nonmetastatic high-risk prostate cancer randomized to lifelong hormone treatment alone or combined with radiotherapy (SPCG VII). *ASCO Meeting Abstracts*, 2014. 32: 4.
<http://meetinglibrary.asco.org/content/123789-142>
461. Warde, P., *et al.* Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*, 2011. 378: 2104.
<https://www.ncbi.nlm.nih.gov/pubmed/22056152>
462. Mason, M.D., *et al.* Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. *J Clin Oncol*, 2015. 33: 2143.
<https://www.ncbi.nlm.nih.gov/pubmed/25691677>
463. Mottet, N., *et al.* Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. *Eur Urol*, 2012. 62: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/22502942>
464. Fizazi, K., *et al.* A phase III trial of docetaxel-estramustine in high-risk localised prostate cancer: a planned analysis of response, toxicity and quality of life in the GETUG 12 trial. *Eur J Cancer*, 2012. 48: 209.
<https://www.ncbi.nlm.nih.gov/pubmed/22119204>
465. Zelefsky, M.J., *et al.* Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. *Eur Urol*, 2011. 60: 1133.
<https://www.ncbi.nlm.nih.gov/pubmed/21889832>
466. Krauss, D., *et al.* Lack of benefit for the addition of androgen deprivation therapy to dose-escalated radiotherapy in the treatment of intermediate- and high-risk prostate cancer. *Int J Radiat Oncol Biol Phys*, 2011. 80: 1064.
<https://www.ncbi.nlm.nih.gov/pubmed/20584576>
467. Kupelian, P.A., *et al.* Effect of increasing radiation doses on local and distant failures in patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys*, 2008. 71: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/17996382>
468. Leibel, S.A., *et al.* The effects of local and regional treatment on the metastatic outcome in prostatic carcinoma with pelvic lymph node involvement. *Int J Radiat Oncol Biol Phys*, 1994. 28: 7.
<https://www.ncbi.nlm.nih.gov/pubmed/8270461>
469. Asbell, S.O., *et al.* Elective pelvic irradiation in stage A2, B carcinoma of the prostate: analysis of RTOG 77-06. *Int J Radiat Oncol Biol Phys*, 1988. 15: 1307.
<https://www.ncbi.nlm.nih.gov/pubmed/3058656>
470. Pommier, P., *et al.* Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol*, 2007. 25: 5366.
<https://www.ncbi.nlm.nih.gov/pubmed/18048817>
471. Roach, M., 3rd, *et al.* Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys*, 1994. 28: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/7505775>
472. Lawton, C.A., *et al.* Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. *J Clin Oncol*, 2005. 23: 800.
<https://www.ncbi.nlm.nih.gov/pubmed/15681524>
473. James, N.D., *et al.* Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*, 2016. 387: 1163.
<https://www.ncbi.nlm.nih.gov/pubmed/26719232>
474. Trofimov, A., *et al.* Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. *Int J Radiat Oncol Biol Phys*, 2007. 69: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/17513063>

475. Vargas, C., *et al.* Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*, 2008. 70: 744.
<https://www.ncbi.nlm.nih.gov/pubmed/17904306>
476. Gray, P.J., *et al.* Patient-reported outcomes after 3-dimensional conformal, intensity-modulated, or proton beam radiotherapy for localized prostate cancer. *Cancer*, 2013. 119: 1729.
<https://www.ncbi.nlm.nih.gov/pubmed/23436283>
477. Sheets, N.C., *et al.* Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *Jama*, 2012. 307: 1611.
<https://www.ncbi.nlm.nih.gov/pubmed/22511689>
478. Yu, J.B., *et al.* Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst*, 2013. 105: 25.
<https://www.ncbi.nlm.nih.gov/pubmed/23243199>
479. Ash, D., *et al.* ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. *Radiother Oncol*, 2000. 57: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/11104892>
480. Salembier, C., *et al.* Tumour and target volumes in permanent prostate brachytherapy: a supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy. *Radiother Oncol*, 2007. 83: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/17321620>
481. Davis, B.J., *et al.* American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy*, 2012. 11: 6.
<https://www.ncbi.nlm.nih.gov/pubmed/22265434>
482. Machtens, S., *et al.* Long-term results of interstitial brachytherapy (LDR-Brachytherapy) in the treatment of patients with prostate cancer. *World J Urol*, 2006. 24: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/16645877>
483. Grimm, P., *et al.* Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU Int*, 2012. 109 Suppl 1: 22.
<https://www.ncbi.nlm.nih.gov/pubmed/22239226>
484. Potters, L., *et al.* Monotherapy for stage T1-T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. *Radiother Oncol*, 2004. 71: 29.
<https://www.ncbi.nlm.nih.gov/pubmed/15066293>
485. Sylvester, J.E., *et al.* Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I(125) prostate brachytherapy in clinically localized prostate cancer: Seattle experience. *Int J Radiat Oncol Biol Phys*, 2011. 81: 376.
<https://www.ncbi.nlm.nih.gov/pubmed/20864269>
486. Potters, L., *et al.* 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol*, 2005. 173: 1562.
<https://www.ncbi.nlm.nih.gov/pubmed/15821486>
487. Stone, N.N., *et al.* Intermediate term biochemical-free progression and local control following 125iodine brachytherapy for prostate cancer. *J Urol*, 2005. 173: 803.
<https://www.ncbi.nlm.nih.gov/pubmed/15711273>
488. Zelefsky, M.J., *et al.* Multi-institutional analysis of long-term outcome for stages T1-T2 prostate cancer treated with permanent seed implantation. *Int J Radiat Oncol Biol Phys*, 2007. 67: 327.
<https://www.ncbi.nlm.nih.gov/pubmed/17084558>
489. Lawton, C.A., *et al.* Results of a phase II trial of transrectal ultrasound-guided permanent radioactive implantation of the prostate for definitive management of localized adenocarcinoma of the prostate (radiation therapy oncology group 98-05). *Int J Radiat Oncol Biol Phys*, 2007. 67: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/17084551>
490. Stock, R.G., *et al.* Importance of post-implant dosimetry in permanent prostate brachytherapy. *Eur Urol*, 2002. 41: 434.
<https://www.ncbi.nlm.nih.gov/pubmed/12074816>
491. Lee, L.N., *et al.* Role of hormonal therapy in the management of intermediate- to high-risk prostate cancer treated with permanent radioactive seed implantation. *Int J Radiat Oncol Biol Phys*, 2002. 52: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/11872291>
492. Morris, W.J., *et al.* *ASCENDE-RT: An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- And Intermediate-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys*.
[http://www.redjournal.org/article/S0360-3016\(16\)33484-8/abstract](http://www.redjournal.org/article/S0360-3016(16)33484-8/abstract)

493. Hoskin, P.J., *et al.* GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: an update. *Radiother Oncol*, 2013. 107: 325.
<https://www.ncbi.nlm.nih.gov/pubmed/23773409>
494. Galalae, R.M., *et al.* Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys*, 2002. 52: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/11777625>
495. Hoskin, P.J., *et al.* Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol*, 2012. 103: 217.
<https://www.ncbi.nlm.nih.gov/pubmed/22341794>
496. Pieters, B.R., *et al.* Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review. *Radiother Oncol*, 2009. 93: 168.
<https://www.ncbi.nlm.nih.gov/pubmed/19748692>
497. Hauswald, H., *et al.* High-Dose-Rate Monotherapy for Localized Prostate Cancer: 10-Year Results. *Int J Radiat Oncol Biol Phys*, 2016. 94: 667.
<https://www.ncbi.nlm.nih.gov/pubmed/26443877>
498. Zamboglou, N., *et al.* High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: treatment evolution and mature results. *Int J Radiat Oncol Biol Phys*, 2013. 85: 672.
<https://www.ncbi.nlm.nih.gov/pubmed/22929859>
499. Wallis, C.J., *et al.* Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. *BMJ*, 2016. 352: i851.
<https://www.ncbi.nlm.nih.gov/pubmed/26936410>
500. Hanks, G.E. External-beam radiation therapy for clinically localized prostate cancer: patterns of care studies in the United States. *NCI Monogr*, 1988: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/3050542>
501. Bolla, M., *et al.* Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet*, 2012. 380: 2018.
<https://www.ncbi.nlm.nih.gov/pubmed/23084481>
502. Wiegel, T., *et al.* Adjuvant Radiotherapy Versus Wait-and-See After Radical Prostatectomy: 10-year Follow-up of the ARO 96-02/AUO AP 09/95 Trial. *Eur Urol*, 2014. 66: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/24680359>
503. Swanson GP, *et al.* Update of SWOG 8794: adjuvant radiotherapy for pT3 prostate cancer improves metastasis free survival. *Int J Rad Oncol Biol Phys* 2008. 72: S31.
[http://www.redjournal.org/article/S0360-3016\(08\)01051-1/abstract](http://www.redjournal.org/article/S0360-3016(08)01051-1/abstract)
504. Thompson, I.M., *et al.* Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol*, 2009. 181: 956.
<https://www.ncbi.nlm.nih.gov/pubmed/19167731>
505. Stephenson, A.J., *et al.* Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol*, 2007. 25: 2035.
<https://www.ncbi.nlm.nih.gov/pubmed/17513807>
506. Wiegel, T., *et al.* Achieving an undetectable PSA after radiotherapy for biochemical progression after radical prostatectomy is an independent predictor of biochemical outcome--results of a retrospective study. *Int J Radiat Oncol Biol Phys*, 2009. 73: 1009.
<https://www.ncbi.nlm.nih.gov/pubmed/18963539>
507. Fahmy, W.E., *et al.* Cryosurgery for prostate cancer. *Arch Androl*, 2003. 49: 397.
<https://www.ncbi.nlm.nih.gov/pubmed/12893518>
508. Rees, J., *et al.* Cryosurgery for prostate cancer. *BJU Int*, 2004. 93: 710.
<https://www.ncbi.nlm.nih.gov/pubmed/15049977>
509. Han, K.R., *et al.* Third-generation cryosurgery for primary and recurrent prostate cancer. *BJU Int*, 2004. 93: 14.
<https://www.ncbi.nlm.nih.gov/pubmed/14678360>
510. Beerlage, H.P., *et al.* Current status of minimally invasive treatment options for localized prostate carcinoma. *Eur Urol*, 2000. 37: 2.
<https://www.ncbi.nlm.nih.gov/pubmed/10671777>
511. Ramsay, C.R., *et al.* Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. *Health Technol Assess*, 2015. 19: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/26140518>

512. Madersbacher, S., *et al.* High-energy shockwaves and extracorporeal high-intensity focused ultrasound. *J Endourol*, 2003. 17: 667.
<https://www.ncbi.nlm.nih.gov/pubmed/14622487>
513. Blana, A., *et al.* High-intensity focused ultrasound for prostate cancer: comparative definitions of biochemical failure. *BJU Int*, 2009. 104: 1058.
<https://www.ncbi.nlm.nih.gov/pubmed/19388986>
514. Aus, G. Current status of HIFU and cryotherapy in prostate cancer--a review. *Eur Urol*, 2006. 50: 927.
<https://www.ncbi.nlm.nih.gov/pubmed/16971038>
515. Mouraviev, V., *et al.* Pathologic basis of focal therapy for early-stage prostate cancer. *Nat Rev Urol*, 2009. 6: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/19352395>
516. Cooperberg, M.R., *et al.* Contemporary trends in low risk prostate cancer: risk assessment and treatment. *J Urol*, 2007. 178: S14.
<https://www.ncbi.nlm.nih.gov/pubmed/17644125>
517. Polascik, T.J., *et al.* Pathologic stage T2a and T2b prostate cancer in the recent prostate-specific antigen era: implications for unilateral ablative therapy. *Prostate*, 2008. 68: 1380.
<https://www.ncbi.nlm.nih.gov/pubmed/18543281>
518. Ahmed, H.U., *et al.* Will focal therapy become a standard of care for men with localized prostate cancer? *Nat Clin Pract Oncol*, 2007. 4: 632.
<https://www.ncbi.nlm.nih.gov/pubmed/17965641>
519. Eggener, S.E., *et al.* Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. *J Urol*, 2007. 178: 2260.
<https://www.ncbi.nlm.nih.gov/pubmed/17936815>
520. Crawford, E.D., *et al.* Targeted focal therapy: a minimally invasive ablation technique for early prostate cancer. *Oncology (Williston Park)*, 2007. 21: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/17313155>
521. Valerio, M., *et al.* New and Established Technology in Focal Ablation of the Prostate: A Systematic Review. *Eur Urol*, 2017. 71: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/27595377>
522. MacLennan, S., *et al.* A core outcome set for localised prostate cancer effectiveness trials: protocol for a systematic review of the literature and stakeholder involvement through interviews and a Delphi survey. *Trials*, 2015. 16: 76.
<https://www.ncbi.nlm.nih.gov/pubmed/25887437>
523. Pagliarulo, V., *et al.* Contemporary role of androgen deprivation therapy for prostate cancer. *Eur Urol*, 2012. 61: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/21871711>
524. Oefelein, M.G., *et al.* Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. *Urology*, 2000. 56: 1021.
<https://www.ncbi.nlm.nih.gov/pubmed/11113751>
525. Morote, J., *et al.* Individual variations of serum testosterone in patients with prostate cancer receiving androgen deprivation therapy. *BJU Int*, 2009. 103: 332.
<https://www.ncbi.nlm.nih.gov/pubmed/19007366>
5261. Pickles, T., *et al.* Incomplete testosterone suppression with luteinizing hormone-releasing hormone agonists: does it happen and does it matter? *BJU Int*, 2012. 110: E500.
<https://www.ncbi.nlm.nih.gov/pubmed/22564197>
527. Klotz, L., *et al.* MP74-01 Nadir Testosterone on ADT predicts for time to castrate resistant progression: A secondary analysis of the PR-7 intermittent vs continuous ADT trial. *J Urol*. 191: e855.
[http://www.jurology.com/article/S0022-5347\(14\)02593-2/abstract](http://www.jurology.com/article/S0022-5347(14)02593-2/abstract)
528. Desmond, A.D., *et al.* Subcapsular orchiectomy under local anaesthesia. Technique, results and implications. *Br J Urol*, 1988. 61: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/3349279>
529. Scherr, D.S., *et al.* The nonsteroidal effects of diethylstilbestrol: the rationale for androgen deprivation therapy without estrogen deprivation in the treatment of prostate cancer. *J Urol*, 2003. 170: 1703.
<https://www.ncbi.nlm.nih.gov/pubmed/14532759>
530. Klotz, L., *et al.* A phase 1-2 trial of diethylstilbestrol plus low dose warfarin in advanced prostate carcinoma. *J Urol*, 1999. 161: 169.
<https://www.ncbi.nlm.nih.gov/pubmed/10037391>

531. Farrugia, D., *et al.* Stilboestrol plus adrenal suppression as salvage treatment for patients failing treatment with luteinizing hormone-releasing hormone analogues and orchidectomy. *BJU Int*, 2000. 85: 1069.
<https://www.ncbi.nlm.nih.gov/pubmed/10848697>
532. Klotz, L., *et al.* The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int*, 2008. 102: 1531.
<https://www.ncbi.nlm.nih.gov/pubmed/19035858>
533. Seidenfeld, J., *et al.* Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med*, 2000. 132: 566.
<https://www.ncbi.nlm.nih.gov/pubmed/10744594>
534. Hedlund, P.O., *et al.* Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. *Scand J Urol Nephrol*, 2008. 42: 220.
<https://www.ncbi.nlm.nih.gov/pubmed/18432528>
535. Bublej, G.J. Is the flare phenomenon clinically significant? *Urology*, 2001. 58: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/11502435>
536. Crawford, E.D., *et al.* A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer. *J Urol*, 2011. 186: 889.
<https://www.ncbi.nlm.nih.gov/pubmed/21788033>
537. Moffat, L.E. Comparison of Zoladex, diethylstilbestrol and cyproterone acetate treatment in advanced prostate cancer. *Eur Urol*, 1990. 18 Suppl 3: 26.
<https://www.ncbi.nlm.nih.gov/pubmed/2151272>
538. Schroder, F.H., *et al.* Metastatic prostate cancer treated by flutamide versus cyproterone acetate. Final analysis of the "European Organization for Research and Treatment of Cancer" (EORTC) Protocol 30892. *Eur Urol*, 2004. 45: 457.
<https://www.ncbi.nlm.nih.gov/pubmed/15041109>
539. Smith, M.R., *et al.* Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. *J Clin Oncol*, 2004. 22: 2546.
<https://www.ncbi.nlm.nih.gov/pubmed/15226323>
540. Iversen, P. Antiandrogen monotherapy: indications and results. *Urology*, 2002. 60: 64.
<https://www.ncbi.nlm.nih.gov/pubmed/12231053>
541. Wadhwa, V.K., *et al.* Long-term changes in bone mineral density and predicted fracture risk in patients receiving androgen-deprivation therapy for prostate cancer, with stratification of treatment based on presenting values. *BJU Int*, 2009. 104: 800.
<https://www.ncbi.nlm.nih.gov/pubmed/19338564>
542. Montgomery, R.B., *et al.* Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res*, 2008. 68: 4447.
<https://www.ncbi.nlm.nih.gov/pubmed/18519708>
543. Bayoumi, A.M., *et al.* Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. *J Natl Cancer Inst*, 2000. 92: 1731.
<https://www.ncbi.nlm.nih.gov/pubmed/11058616>
544. James, N.D., *et al.* Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). *Eur Urol*, 2015. 67: 1028.
<https://www.ncbi.nlm.nih.gov/pubmed/25301760>
545. Glass, T.R., *et al.* Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. *J Urol*, 2003. 169: 164.
<https://www.ncbi.nlm.nih.gov/pubmed/12478127>
546. Gravis, G., *et al.* Prognostic Factors for Survival in Noncastrate Metastatic Prostate Cancer: Validation of the Glass Model and Development of a Novel Simplified Prognostic Model. *Eur Urol*, 2015. 68: 196.
<https://www.ncbi.nlm.nih.gov/pubmed/25277272>
547. Sweeney, C.J., *et al.* Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med*, 2015. 373: 737.
<https://www.ncbi.nlm.nih.gov/pubmed/26244877>
548. Hussain, M., *et al.* Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). *J Clin Oncol*, 2006. 24: 3984.
<https://www.ncbi.nlm.nih.gov/pubmed/16921051>

549. Tsushima, T., *et al.* Optimal starting time for flutamide to prevent disease flare in prostate cancer patients treated with a gonadotropin-releasing hormone agonist. *Urol Int*, 2001. 66: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/11316974>
550. Collette, L., *et al.* Why phase III trials of maximal androgen blockade versus castration in M1 prostate cancer rarely show statistically significant differences. *Prostate*, 2001. 48: 29.
<https://www.ncbi.nlm.nih.gov/pubmed/11391684>
551. Eisenberger, M.A., *et al.* Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med*, 1998. 339: 1036.
<https://www.ncbi.nlm.nih.gov/pubmed/9761805>
552. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet*, 2000. 355: 1491.
<https://www.ncbi.nlm.nih.gov/pubmed/10801170>
553. Schmitt, B., *et al.* Maximal androgen blockade for advanced prostate cancer. *Cochrane Database Syst Rev*, 2000: Cd001526.
<https://www.ncbi.nlm.nih.gov/pubmed/10796804>
554. Akaza, H., *et al.* Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. *Cancer*, 2009. 115: 3437.
<https://www.ncbi.nlm.nih.gov/pubmed/19536889>
555. Kunath, F., *et al.* Non-steroidal antiandrogen monotherapy compared with luteinising hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. *Cochrane Database Syst Rev*, 2014. 6: CD009266.
<https://www.ncbi.nlm.nih.gov/pubmed/24979481>
556. Niraula, S., *et al.* Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. *J Clin Oncol*, 2013. 31: 2029.
<https://www.ncbi.nlm.nih.gov/pubmed/23630216>
557. Sciarra, A., *et al.* A novel therapeutic option for castration-resistant prostate cancer: after or before chemotherapy? *Eur Urol*, 2014. 65: 905.
<https://www.ncbi.nlm.nih.gov/pubmed/23838638>
558. Botrel, T.E., *et al.* Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. *BMC Urol*, 2014. 14: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/24460605>
559. Brungs, D., *et al.* Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: results from a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*, 2014. 17: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/24686773>
560. Magnan, S., *et al.* Intermittent vs Continuous Androgen Deprivation Therapy for Prostate Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol*, 2015. 1: 1261.
<https://www.ncbi.nlm.nih.gov/pubmed/26378418>
561. Hussain, M., *et al.* Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med*, 2013. 368: 1314.
<https://www.ncbi.nlm.nih.gov/pubmed/23550669>
562. Hussain, M., *et al.* Evaluating Intermittent Androgen-Deprivation Therapy Phase III Clinical Trials: The Devil Is in the Details. *J Clin Oncol*, 2016. 34: 280
<https://www.ncbi.nlm.nih.gov/pubmed/26552421>
563. Verhagen, P.C., *et al.* Intermittent versus continuous cyproterone acetate in bone metastatic prostate cancer: results of a randomized trial. *World J Urol*, 2014. 32: 1287.
<https://www.ncbi.nlm.nih.gov/pubmed/24258313>
564. Calais da Silva, F., *et al.* Locally advanced and metastatic prostate cancer treated with intermittent androgen monotherapy or maximal androgen blockade: results from a randomised phase 3 study by the South European Urooncological Group. *Eur Urol*, 2014. 66: 232.
<https://www.ncbi.nlm.nih.gov/pubmed/23582949>
565. Higano, C., *et al.* Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. *Urology*, 2004. 64: 1182.
<https://www.ncbi.nlm.nih.gov/pubmed/15596194>
566. Hershman, D.L., *et al.* Adverse Health Events Following Intermittent and Continuous Androgen Deprivation in Patients With Metastatic Prostate Cancer. *JAMA Oncol*, 2015: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/26720308>

567. Abrahamsson, P.A. Potential benefits of intermittent androgen suppression therapy in the treatment of prostate cancer: a systematic review of the literature. *Eur Urol*, 2010. 57: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/19683858>
568. Nair, B., *et al.* Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. *Cochrane Database Syst Rev*, 2002: Cd003506.
<https://www.ncbi.nlm.nih.gov/pubmed/11869665>
569. Gravis, G., *et al.* Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol*, 2013. 14: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/23306100>
570. Gravis G., *et al.* Androgen deprivation therapy (ADT) plus docetaxel (D) versus ADT alone for hormone-naïve metastatic prostate cancer (PCa): Long-term analysis of the GETUG-AFU 15 phase III trial. *J Clin Oncol* 33, 2015 (suppl 7; abstr 140), 2015.
<http://meetinglibrary.asco.org/content/141485-159>
571. Vale, C.L., *et al.* Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26718929>
572. Smith, T.J., *et al.* Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*, 2015. 33: 3199.
<https://www.ncbi.nlm.nih.gov/pubmed/26169616>
573. Culp, S.H., *et al.* Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. *Eur Urol*, 2014. 65: 1058.
<https://www.ncbi.nlm.nih.gov/pubmed/24290503>
574. Gratzke, C., *et al.* Role of radical prostatectomy in metastatic prostate cancer: data from the Munich Cancer Registry. *Eur Urol*, 2014. 66: 602.
<https://www.ncbi.nlm.nih.gov/pubmed/24821581>
575. Heidenreich, A., *et al.* Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. *J Urol*, 2015. 193: 832.
<https://www.ncbi.nlm.nih.gov/pubmed/25254935>
576. Ost, P., *et al.* Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. *Eur Urol*, 2015. 67: 852.
<https://www.ncbi.nlm.nih.gov/pubmed/25240974>
577. Lecouvet, F.E., *et al.* Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: a review and position statement by the European Organisation for Research and Treatment of Cancer imaging group. *Eur J Cancer*, 2014. 50: 2519.
<https://www.ncbi.nlm.nih.gov/pubmed/25139492>
578. Padhani, A.R., *et al.* Rationale for Modernising Imaging in Advanced Prostate Cancer. *European Urology Focus*.
[http://www.europeanurology.com/article/S2405-4569\(16\)30097-9/abstract/rationale-for-modernising-imaging-in-advanced-prostate-cancer](http://www.europeanurology.com/article/S2405-4569(16)30097-9/abstract/rationale-for-modernising-imaging-in-advanced-prostate-cancer)
579. Ulmert, D., *et al.* A novel automated platform for quantifying the extent of skeletal tumour involvement in prostate cancer patients using the Bone Scan Index. *Eur Urol*, 2012. 62: 78.
<https://www.ncbi.nlm.nih.gov/pubmed/22306323>
580. Scher, H.I., *et al.* Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*, 2016. 34: 1402.
<https://www.ncbi.nlm.nih.gov/pubmed/26903579>
581. Smith, B.D., *et al.* Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol*, 2009. 27: 2758.
<https://www.ncbi.nlm.nih.gov/pubmed/19403886>
582. Arnold, M., *et al.* Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. *Eur J Cancer*, 2015. 51: 1164.
<https://www.ncbi.nlm.nih.gov/pubmed/24120180>
583. Ries, LAG. *et al.* eds. SEER cancer Statistics Review, 1975-2005. 2008.
https://seer.cancer.gov/archive/csr/1975_2005/
584. Scosyrev, E., *et al.* Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. *Cancer*, 2012. 118: 3062.
<https://www.ncbi.nlm.nih.gov/pubmed/22006014>

585. Richstone, L., *et al.* Radical prostatectomy in men aged ≥ 70 years: effect of age on upgrading, upstaging, and the accuracy of a preoperative nomogram. *BJU Int*, 2008. 101: 541.
<https://www.ncbi.nlm.nih.gov/pubmed/18257855>
586. Sun, L., *et al.* Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras. *J Urol*, 2009. 182: 2242.
<https://www.ncbi.nlm.nih.gov/pubmed/19758616>
587. Bubolz, T., *et al.* Treatments for prostate cancer in older men: 1984-1997. *Urology*, 2001. 58: 977.
<https://www.ncbi.nlm.nih.gov/pubmed/11744472>
588. Houterman, S., *et al.* Impact of comorbidity on treatment and prognosis of prostate cancer patients: a population-based study. *Crit Rev Oncol Hematol*, 2006. 58: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/16213153>
589. Hamilton, A.S., *et al.* Trends in the treatment of localized prostate cancer using supplemented cancer registry data. *BJU Int*, 2011. 107: 576.
<https://www.ncbi.nlm.nih.gov/pubmed/20735387>
590. Tewari, A., *et al.* Long-term survival probability in men with clinically localized prostate cancer: a case-control, propensity modeling study stratified by race, age, treatment and comorbidities. *J Urol*, 2004. 171: 1513.
<https://www.ncbi.nlm.nih.gov/pubmed/15017210>
591. Parmelee, P.A., *et al.* Validation of the Cumulative Illness Rating Scale in a geriatric residential population. *J Am Geriatr Soc*, 1995. 43: 130.
<https://www.ncbi.nlm.nih.gov/pubmed/7836636>
592. Groome, P.A., *et al.* Assessing the impact of comorbid illnesses on death within 10 years in prostate cancer treatment candidates. *Cancer*, 2011. 117: 3943.
<https://www.ncbi.nlm.nih.gov/pubmed/21858801>
593. Katz, S., *et al.* Studies of Illness in the Aged. The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. *JAMA*, 1963. 185: 914.
<https://www.ncbi.nlm.nih.gov/pubmed/14044222>
594. Lawton, M.P., *et al.* Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*, 1969. 9: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/5349366>
595. Stineman, M.G., *et al.* All-cause 1-, 5-, and 10-year mortality in elderly people according to activities of daily living stage. *J Am Geriatr Soc*, 2012. 60: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/22352414>
596. Blanc-Bisson, C., *et al.* Undernutrition in elderly patients with cancer: target for diagnosis and intervention. *Crit Rev Oncol Hematol*, 2008. 67: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/18554922>
597. Sachs, G.A., *et al.* Cognitive impairment: an independent predictor of excess mortality: a cohort study. *Ann Intern Med*, 2011. 155: 300.
<https://www.ncbi.nlm.nih.gov/pubmed/21893623>
598. Robinson, T.N., *et al.* Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. *J Am Coll Surg*, 2012. 215: 12.
<https://www.ncbi.nlm.nih.gov/pubmed/22626912>
599. Droz, J.P., *et al.* Management of Prostate Cancer in Elderly Patients: Recommendations of a Task Force of the International Society of Geriatric Oncology. *Eur Urol*, 2017.
<https://www.ncbi.nlm.nih.gov/pubmed/28089304>
600. Borson, S., *et al.* The Mini-Cog as a screen for dementia: validation in a population-based sample. *J Am Geriatr Soc*, 2003. 51: 1451.
<https://www.ncbi.nlm.nih.gov/pubmed/14511167>
601. Oken, M.M., *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*, 1982. 5: 649.
<https://www.ncbi.nlm.nih.gov/pubmed/7165009>
602. Bellera, C.A., *et al.* Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol*, 2012. 23: 2166.
<https://www.ncbi.nlm.nih.gov/pubmed/22250183>
603. Liu, D., *et al.* Active surveillance versus surgery for low risk prostate cancer: a clinical decision analysis. *J Urol*, 2012. 187: 1241.
<https://www.ncbi.nlm.nih.gov/pubmed/22335873>
604. Begg, C.B., *et al.* Variations in morbidity after radical prostatectomy. *N Engl J Med*, 2002. 346: 1138.
<https://www.ncbi.nlm.nih.gov/pubmed/11948274>

605. Stanford, J.L., *et al.* Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. *JAMA*, 2000. 283: 354.
<https://www.ncbi.nlm.nih.gov/pubmed/10647798>
606. Kupelian, P.A., *et al.* Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. *J Clin Oncol*, 2002. 20: 3376.
<https://www.ncbi.nlm.nih.gov/pubmed/12177097>
607. Studer, U.E., *et al.* Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. *J Clin Oncol*, 2006. 24: 1868.
<https://www.ncbi.nlm.nih.gov/pubmed/16622261>
608. Aapro, M., *et al.* Bone-modifying agents in the treatment of bone metastases in patients with advanced genitourinary malignancies: a focus on zoledronic acid. *Ther Adv Urol*, 2012. 4: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/22496711>
609. Berthold, D.R., *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol*, 2008. 26: 242.
<https://www.ncbi.nlm.nih.gov/pubmed/18182665>
610. Italiano, A., *et al.* Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration-resistant prostate cancer. *Eur Urol*, 2009. 55: 1368.
<https://www.ncbi.nlm.nih.gov/pubmed/18706755>
611. de Bono, J.S., *et al.* Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*, 2011. 364: 1995.
<https://www.ncbi.nlm.nih.gov/pubmed/21612468>
612. Scher, H.I., *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*, 2012. 367: 1187.
<https://www.ncbi.nlm.nih.gov/pubmed/22894553>
613. de Bono, J.S., *et al.* Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*, 2010. 376: 1147.
<https://www.ncbi.nlm.nih.gov/pubmed/20888992>
614. Fizazi, K., *et al.* Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*, 2012. 13: 983.
<https://www.ncbi.nlm.nih.gov/pubmed/22995653>
615. Kantoff, P.W., *et al.* Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*, 2010. 363: 411.
<https://www.ncbi.nlm.nih.gov/pubmed/20818862>
616. Sternberg, C.N., *et al.* Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. *Ann Oncol*, 2014. 25: 429.
<https://www.ncbi.nlm.nih.gov/pubmed/24478320>
617. Bahl, A., *et al.* Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. *Ann Oncol*, 2013. 24: 2402.
<https://www.ncbi.nlm.nih.gov/pubmed/23723295>
618. Moul, J.W. Prostate specific antigen only progression of prostate cancer. *J Urol*, 2000. 163: 1632.
<https://www.ncbi.nlm.nih.gov/pubmed/10799151>
619. Amling, C.L., *et al.* Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? *J Urol*, 2001. 165: 1146.
<https://www.ncbi.nlm.nih.gov/pubmed/11257657>
620. Toussi, A., *et al.* Standardizing the Definition of Biochemical Recurrence after Radical Prostatectomy-What Prostate Specific Antigen Cut Point Best Predicts a Durable Increase and Subsequent Systemic Progression? *J Urol*, 2016. 195: 1754.
<https://www.ncbi.nlm.nih.gov/pubmed/26721226>
621. Roach, M., 3rd, *et al.* Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*, 2006. 65: 965.
<https://www.ncbi.nlm.nih.gov/pubmed/16798415>

622. Boorjian, S.A., *et al.* Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. *Eur Urol*, 2011. 59: 893.
<https://www.ncbi.nlm.nih.gov/pubmed/21388736>
623. Antonarakis, E.S., *et al.* The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int*, 2012. 109: 32.
<https://www.ncbi.nlm.nih.gov/pubmed/21777360>
624. Brockman, J.A., *et al.* Nomogram Predicting Prostate Cancer-specific Mortality for Men with Biochemical Recurrence After Radical Prostatectomy. *Eur Urol*, 2015. 67: 1160.
<https://www.ncbi.nlm.nih.gov/pubmed/25301759>
625. D'Amico, A.V., *et al.* Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. *J Urol*, 2004. 172: S42.
<https://www.ncbi.nlm.nih.gov/pubmed/15535442>
626. Freedland, S.J., *et al.* Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *Jama*, 2005. 294: 433.
<https://www.ncbi.nlm.nih.gov/pubmed/16046649>
627. Briganti, A., *et al.* Prediction of outcome following early salvage radiotherapy among patients with biochemical recurrence after radical prostatectomy. *Eur Urol*, 2014. 66: 479.
<https://www.ncbi.nlm.nih.gov/pubmed/24345725>
628. Trock, B.J., *et al.* Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *Jama*, 2008. 299: 2760.
<https://www.ncbi.nlm.nih.gov/pubmed/18560003>
629. Denham, J.W., *et al.* Time to biochemical failure and prostate-specific antigen doubling time as surrogates for prostate cancer-specific mortality: evidence from the TROG 96.01 randomised controlled trial. *Lancet Oncol*, 2008. 9: 1058.
<https://www.ncbi.nlm.nih.gov/pubmed/18929505>
630. Zumsteg, Z.S., *et al.* The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. *Eur Urol*, 2015. 67: 1009.
<https://www.ncbi.nlm.nih.gov/pubmed/25308970>
631. Rouviere, O., *et al.* Imaging of prostate cancer local recurrences: why and how? *Eur Radiol*, 2010. 20: 1254.
<https://www.ncbi.nlm.nih.gov/pubmed/19921202>
632. Beresford, M.J., *et al.* A systematic review of the role of imaging before salvage radiotherapy for post-prostatectomy biochemical recurrence. *Clin Oncol (R Coll Radiol)*, 2010. 22: 46.
<https://www.ncbi.nlm.nih.gov/pubmed/19948393>
633. Gomez, P., *et al.* Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? *BJU Int*, 2004. 94: 299.
<https://www.ncbi.nlm.nih.gov/pubmed/15291855>
634. Kane, C.J., *et al.* Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. *Urology*, 2003. 61: 607.
<https://www.ncbi.nlm.nih.gov/pubmed/12639656>
635. Evangelista, L., *et al.* Choline PET or PET/CT and biochemical relapse of prostate cancer: a systematic review and meta-analysis. *Clin Nucl Med*, 2013. 38: 305.
<https://www.ncbi.nlm.nih.gov/pubmed/23486334>
636. Fanti, S., *et al.* PET/CT with (11)C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. *Eur J Nucl Med Mol Imaging*, 2016. 43: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/26450693>
637. Fuccio, C., *et al.* Role of ¹¹C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. *Ann Nucl Med*, 2010. 24: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/20544323>
638. Fuccio, C., *et al.* Role of ¹¹C-choline PET/CT in the re-staging of prostate cancer patients with biochemical relapse and negative results at bone scintigraphy. *Eur J Radiol*, 2012. 81: e893.
<https://www.ncbi.nlm.nih.gov/pubmed/22621862>
639. Treglia, G., *et al.* Relationship between prostate-specific antigen kinetics and detection rate of radiolabelled choline PET/CT in restaging prostate cancer patients: a meta-analysis. *Clin Chem Lab Med*, 2014. 52: 725.
<https://www.ncbi.nlm.nih.gov/pubmed/24310773>

640. Calabria, F., *et al.* The optimal timing to perform $^{18}\text{F}/^{11}\text{C}$ -choline PET/CT in patients with suspicion of relapse of prostate cancer: trigger PSA versus PSA velocity and PSA doubling time. *Int J Biol Markers*, 2014: 0.
<https://www.ncbi.nlm.nih.gov/pubmed/24474456>
641. Castellucci, P., *et al.* Early Biochemical Relapse After Radical Prostatectomy: Which Prostate Cancer Patients May Benefit from a Restaging ^{11}C -Choline PET/CT Scan Before Salvage Radiation Therapy? *J Nucl Med*, 2014. 55: 1424.
<https://www.ncbi.nlm.nih.gov/pubmed/24935990>
642. Mitchell, C.R., *et al.* Operational characteristics of (^{11}C) -choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment. *J Urol*, 2013. 189: 1308.
<https://www.ncbi.nlm.nih.gov/pubmed/23123372>
643. Soyka, J.D., *et al.* Clinical impact of ^{18}F -choline PET/CT in patients with recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*, 2012. 39: 936.
<https://www.ncbi.nlm.nih.gov/pubmed/22415598>
644. Ceci, F., *et al.* Impact of ^{11}C -choline PET/CT on clinical decision making in recurrent prostate cancer: results from a retrospective two-centre trial. *Eur J Nucl Med Mol Imaging*, 2014. 41: 2222.
<https://www.ncbi.nlm.nih.gov/pubmed/25182750>
645. Graziani, T., *et al.* (^{11}C) -Choline PET/CT for restaging prostate cancer. Results from 4,426 scans in a single-centre patient series. *Eur J Nucl Med Mol Imaging*, 2016. 43: 1971.
<https://www.ncbi.nlm.nih.gov/pubmed/27277279>
646. Castellucci, P., *et al.* ^{11}C -choline PET/CT and PSA kinetics. *Eur J Nucl Med Mol Imaging*, 2013. 40 Suppl 1: S36.
<https://www.ncbi.nlm.nih.gov/pubmed/23579864>
647. Chondrogiannis, S., *et al.* Role of (^{18}F) -choline PET/CT in suspicion of relapse following definitive radiotherapy for prostate cancer. *Eur J Nucl Med Mol Imaging*, 2013. 40: 1356.
<https://www.ncbi.nlm.nih.gov/pubmed/23670521>
648. Ceci, F., *et al.* ^{11}C -choline PET/CT detects the site of relapse in the majority of prostate cancer patients showing biochemical recurrence after EBRT. *Eur J Nucl Med Mol Imaging*, 2014. 41: 878.
<https://www.ncbi.nlm.nih.gov/pubmed/24346416>
649. Beer, A.J., *et al.* Radionuclide and hybrid imaging of recurrent prostate cancer. *Lancet Oncol*, 2011. 12: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/20599424>
650. Beheshti, M., *et al.* Detection of bone metastases in patients with prostate cancer by ^{18}F fluorocholine and ^{18}F fluoride PET-CT: a comparative study. *Eur J Nucl Med Mol Imaging*, 2008. 35: 1766.
<https://www.ncbi.nlm.nih.gov/pubmed/18465129>
651. Morigi, J.J., *et al.* Prospective Comparison of ^{18}F -Fluoromethylcholine Versus ^{68}Ga -PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. *J Nucl Med*, 2015. 56: 1185.
<https://www.ncbi.nlm.nih.gov/pubmed/26112024>
652. Afshar-Oromieh, A., *et al.* Comparison of PET imaging with a (^{68}Ga) -labelled PSMA ligand and (^{18}F) -choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging*, 2014. 41: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/24072344>
653. Eiber, M., *et al.* Whole-body MRI including diffusion-weighted imaging (DWI) for patients with recurring prostate cancer: technical feasibility and assessment of lesion conspicuity in DWI. *J Magn Reson Imaging*, 2011. 33: 1160.
<https://www.ncbi.nlm.nih.gov/pubmed/21509875>
654. Kitajima, K., *et al.* Detection of recurrent prostate cancer after radical prostatectomy: comparison of ^{11}C -choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. *J Nucl Med*, 2014. 55: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/24434294>
655. van Leeuwen, P.J., *et al.* (^{68}Ga) -PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. *BJU Int*, 2016. 117: 732.
<https://www.ncbi.nlm.nih.gov/pubmed/26683282>

656. Cirillo, S., *et al.* Endorectal magnetic resonance imaging at 1.5 Tesla to assess local recurrence following radical prostatectomy using T2-weighted and contrast-enhanced imaging. *Eur Radiol*, 2009. 19: 761.
<https://www.ncbi.nlm.nih.gov/pubmed/18825386>
657. Sciarra, A., *et al.* Role of Dynamic Contrast-Enhanced Magnetic Resonance (MR) Imaging and Proton MR Spectroscopic Imaging in the Detection of Local Recurrence after Radical Prostatectomy for Prostate Cancer. *Eur Urol*, 2008. 54: 589.
<https://www.ncbi.nlm.nih.gov/pubmed/18226441>
658. Casciani, E., *et al.* Endorectal and dynamic contrast-enhanced MRI for detection of local recurrence after radical prostatectomy. *AJR Am J Roentgenol*, 2008. 190: 1187.
<https://www.ncbi.nlm.nih.gov/pubmed/18430830>
659. Cha, D., *et al.* Evaluation of suspected soft tissue lesion in the prostate bed after radical prostatectomy using 3T multiparametric magnetic resonance imaging. *Magn Reson Imaging*, 2015. 33: 407.
<https://www.ncbi.nlm.nih.gov/pubmed/25527395>
660. Liauw, S.L., *et al.* Evaluation of the prostate bed for local recurrence after radical prostatectomy using endorectal magnetic resonance imaging. *Int J Radiat Oncol Biol Phys*, 2013. 85: 378.
<https://www.ncbi.nlm.nih.gov/pubmed/22717242>
661. Linder, B.J., *et al.* Early localization of recurrent prostate cancer after prostatectomy by endorectal coil magnetic resonance imaging. *Can J Urol*, 2014. 21: 7283.
<https://www.ncbi.nlm.nih.gov/pubmed/24978358>
662. Donati, O.F., *et al.* Multiparametric prostate MR imaging with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences: are all pulse sequences necessary to detect locally recurrent prostate cancer after radiation therapy? *Radiology*, 2013. 268: 440.
<https://www.ncbi.nlm.nih.gov/pubmed/23481164>
663. Abd-Alazeez, M., *et al.* Multiparametric MRI for detection of radiorecurrent prostate cancer: added value of apparent diffusion coefficient maps and dynamic contrast-enhanced images. *Prostate Cancer Prostatic Dis*, 2015. 18: 128.
<https://www.ncbi.nlm.nih.gov/pubmed/25644248>
664. Alonzo, F., *et al.* Detection of locally radio-recurrent prostate cancer at multiparametric MRI: Can dynamic contrast-enhanced imaging be omitted? *Diagn Interv Imaging*, 2016. 97: 433.
<https://www.ncbi.nlm.nih.gov/pubmed/26928245>
665. Parker, W.P., *et al.* Identification of Site-specific Recurrence Following Primary Radiation Therapy for Prostate Cancer Using C-11 Choline Positron Emission Tomography/Computed Tomography: A Nomogram for Predicting Extrapelvic Disease. *Eur Urol*, 2017. 71: 340.
<https://www.ncbi.nlm.nih.gov/pubmed/27597240>
666. Pfister, D., *et al.* Early salvage radiotherapy following radical prostatectomy. *Eur Urol*, 2014. 65: 1034.
<https://www.ncbi.nlm.nih.gov/pubmed/23972524>
667. Siegmann, A., *et al.* Salvage radiotherapy after prostatectomy - what is the best time to treat? *Radiother Oncol*, 2012. 103: 239.
<https://www.ncbi.nlm.nih.gov/pubmed/22119375>
668. Ohri, N., *et al.* Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling. *Eur J Cancer*, 2012. 48: 837.
<https://www.ncbi.nlm.nih.gov/pubmed/21945099>
669. Siegmann, A., *et al.* Dose escalation for patients with decreasing PSA during radiotherapy for elevated PSA after radical prostatectomy improves biochemical progression-free survival: results of a retrospective study. *Strahlenther Onkol*, 2011. 187: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/21786112>
670. Goenka, A., *et al.* Long-term outcomes after high-dose postprostatectomy salvage radiation treatment. *Int J Radiat Oncol Biol Phys*, 2012. 84: 112.
<https://www.ncbi.nlm.nih.gov/pubmed/22300563>
671. Cremers, R.G., *et al.* Efficacy and tolerance of salvage radiotherapy after radical prostatectomy, with emphasis on high-risk patients suited for adjuvant radiotherapy. *Radiother Oncol*, 2010. 97: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/20817287>
672. Bernard, J.R., Jr., *et al.* Salvage radiotherapy for rising prostate-specific antigen levels after radical prostatectomy for prostate cancer: dose-response analysis. *Int J Radiat Oncol Biol Phys*, 2010. 76: 735.
<https://www.ncbi.nlm.nih.gov/pubmed/19464818>

673. Buskirk, S.J., *et al.* Salvage radiotherapy for isolated prostate specific antigen increase after radical prostatectomy: evaluation of prognostic factors and creation of a prognostic scoring system. *J Urol*, 2006. 176: 985.
<https://www.ncbi.nlm.nih.gov/pubmed/16890677>
674. Pazona, J.F., *et al.* Salvage radiation therapy for prostate specific antigen progression following radical prostatectomy: 10-year outcome estimates. *J Urol*, 2005. 174: 1282.
<https://www.ncbi.nlm.nih.gov/pubmed/16145393>
675. Pisansky, T.M., *et al.* Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer. *J Urol*, 2000. 163: 845.
<https://www.ncbi.nlm.nih.gov/pubmed/10687990>
676. Soto, D.E., *et al.* Concurrent androgen deprivation therapy during salvage prostate radiotherapy improves treatment outcomes in high-risk patients. *Int J Radiat Oncol Biol Phys*, 2012. 82: 1227.
<https://www.ncbi.nlm.nih.gov/pubmed/21549519>
677. Shipley, W., *et al.* Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. *N Engl J Med*, 2017. 376: 417.
<http://www.nejm.org/doi/full/10.1056/NEJMoa1607529>
678. Carrie, C., *et al.* Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol*, 2016. 17: 747.
<https://www.ncbi.nlm.nih.gov/pubmed/27160475>
679. Valicenti, R.K., *et al.* Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. *Int J Radiat Oncol Biol Phys*, 2013. 86: 822.
<https://www.ncbi.nlm.nih.gov/pubmed/23845839>
680. King, C.R. The timing of salvage radiotherapy after radical prostatectomy: a systematic review. *Int J Radiat Oncol Biol Phys*, 2012. 84: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/22795730>
681. King, C.R., *et al.* Radiotherapy after prostatectomy: is the evidence for dose escalation out there? *Int J Radiat Oncol Biol Phys*, 2008. 71: 346.
<https://www.ncbi.nlm.nih.gov/pubmed/18234451>
682. Goenka, A., *et al.* Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. *Eur Urol*, 2011. 60: 1142.
<https://www.ncbi.nlm.nih.gov/pubmed/21855208>
683. Ost, P., *et al.* High-dose salvage intensity-modulated radiotherapy with or without androgen deprivation after radical prostatectomy for rising or persisting prostate-specific antigen: 5-year results. *Eur Urol*, 2011. 60: 842.
<https://www.ncbi.nlm.nih.gov/pubmed/21514039>
684. Briganti, A., *et al.* Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. *Eur Urol*, 2012. 62: 472.
<https://www.ncbi.nlm.nih.gov/pubmed/22633803>
685. van den Bergh, R.C., *et al.* Role of Hormonal Treatment in Prostate Cancer Patients with Nonmetastatic Disease Recurrence After Local Curative Treatment: A Systematic Review. *Eur Urol*, 2016. 69: 802.
<https://www.ncbi.nlm.nih.gov/pubmed/26691493>
686. Duchesne, G.M., *et al.* Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol*, 2016. 17: 727.
<https://www.ncbi.nlm.nih.gov/pubmed/27155740>
687. Siddiqui, S.A., *et al.* Timing of androgen deprivation therapy and its impact on survival after radical prostatectomy: a matched cohort study. *J Urol*, 2008. 179: 1830.
<https://www.ncbi.nlm.nih.gov/pubmed/18353378>
688. Crook, J.M., *et al.* Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med*, 2012. 367: 895.
<https://www.ncbi.nlm.nih.gov/pubmed/22931259>
689. Levine, G.N., *et al.* Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation*, 2010. 121: 833.
<https://www.ncbi.nlm.nih.gov/pubmed/20124128>

690. O'Farrell, S., *et al.* Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer. *J Clin Oncol*, 2015. 33: 1243.
<http://jco.ascopubs.org/content/33/11/1243.abstract>
691. Heidenreich, A., *et al.* [Radical salvage prostatectomy : Treatment of local recurrence of prostate cancer after radiotherapy]. *Urologe A*, 2008. 47: 1441.
<https://www.ncbi.nlm.nih.gov/pubmed/18806991>
692. Ahlering, T.E., *et al.* Salvage surgery plus androgen deprivation for radioresistant prostatic adenocarcinoma. *J Urol*, 1992. 147: 900.
<https://www.ncbi.nlm.nih.gov/pubmed/1538492>
693. Zincke, H. Radical prostatectomy and exenterative procedures for local failure after radiotherapy with curative intent: comparison of outcomes. *J Urol*, 1992. 147: 894.
<https://www.ncbi.nlm.nih.gov/pubmed/1538491>
694. Lerner, S.E., *et al.* Critical evaluation of salvage surgery for radio-recurrent/resistant prostate cancer. *J Urol*, 1995. 154: 1103.
<https://www.ncbi.nlm.nih.gov/pubmed/7543608>
695. Rogers, E., *et al.* Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. *J Urol*, 1995. 153: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/7526002>
696. Garzotto, M., *et al.* Androgen deprivation with salvage surgery for radiorecurrent prostate cancer: results at 5-year followup. *J Urol*, 1998. 159: 950.
<https://www.ncbi.nlm.nih.gov/pubmed/9474190>
697. Vaidya, A., *et al.* Salvage radical prostatectomy for radiorecurrent prostate cancer: morbidity revisited. *J Urol*, 2000. 164: 1998.
<https://www.ncbi.nlm.nih.gov/pubmed/11061900>
698. Stephenson, A.J., *et al.* Morbidity and functional outcomes of salvage radical prostatectomy for locally recurrent prostate cancer after radiation therapy. *J Urol*, 2004. 172: 2239.
<https://www.ncbi.nlm.nih.gov/pubmed/15538239>
699. Heidenreich, A., *et al.* [Functional and oncological outcome of salvage prostatectomy of locally recurrent prostate cancer following radiation therapy]. *Urologe A*, 2006. 45: 474.
<https://www.ncbi.nlm.nih.gov/pubmed/16465521>
700. Heidenreich, A., *et al.* Prognostic parameters, complications, and oncologic and functional outcome of salvage radical prostatectomy for locally recurrent prostate cancer after 21st-century radiotherapy. *Eur Urol*, 2010. 57: 437.
<https://www.ncbi.nlm.nih.gov/pubmed/19303197>
701. Chade, D.C., *et al.* Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. *Eur Urol*, 2012. 61: 961.
<https://www.ncbi.nlm.nih.gov/pubmed/22280856>
702. Sanderson, K.M., *et al.* Salvage radical prostatectomy: quality of life outcomes and long-term oncological control of radiorecurrent prostate cancer. *J Urol*, 2006. 176: 2025.
<https://www.ncbi.nlm.nih.gov/pubmed/17070244>
703. Leonardo, C., *et al.* Salvage radical prostatectomy for recurrent prostate cancer after radiation therapy. *Int J Urol*, 2009. 16: 584.
<https://www.ncbi.nlm.nih.gov/pubmed/19453762>
704. Chade, D.C., *et al.* Salvage radical prostatectomy for radiation-recurrent prostate cancer: a multi-institutional collaboration. *Eur Urol*, 2011. 60: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/21420229>
705. Gotto, G.T., *et al.* Impact of prior prostate radiation on complications after radical prostatectomy. *J Urol*, 2010. 184: 136.
<https://www.ncbi.nlm.nih.gov/pubmed/20478594>
706. Ward, J.F., *et al.* Salvage surgery for radiorecurrent prostate cancer: contemporary outcomes. *J Urol*, 2005. 173: 1156.
<https://www.ncbi.nlm.nih.gov/pubmed/15758726>
707. Philippou, Y., *et al.* Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Nonsurgical Therapies for Radiorecurrent Prostate Cancer: A Meta-Regression Analysis. *European Urology Focus*, 2016. 2: 158.
[http://www.europeanurology.com/article/S2405-4569\(15\)00141-8/abstract/](http://www.europeanurology.com/article/S2405-4569(15)00141-8/abstract/)
708. Ismail, M., *et al.* Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. *BJU Int*, 2007. 100: 760.
<https://www.ncbi.nlm.nih.gov/pubmed/17662081>

709. Pisters, L.L., *et al.* Salvage prostate cryoablation: initial results from the cryo on-line data registry. *J Urol*, 2008. 180: 559.
<https://www.ncbi.nlm.nih.gov/pubmed/18554664>
710. Pisters, L.L., *et al.* Locally recurrent prostate cancer after initial radiation therapy: a comparison of salvage radical prostatectomy versus cryotherapy. *J Urol*, 2009. 182: 517.
<https://www.ncbi.nlm.nih.gov/pubmed/19524984>
711. Bahn, D.K., *et al.* Salvage cryosurgery for recurrent prostate cancer after radiation therapy: a seven-year follow-up. *Clin Prostate Cancer*, 2003. 2: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/15040872>
712. Williams, A.K., *et al.* Disease-free survival following salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. *Eur Urol*, 2011. 60: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/21185115>
713. Spiess, P.E., *et al.* A pretreatment nomogram predicting biochemical failure after salvage cryotherapy for locally recurrent prostate cancer. *BJU Int*, 2010. 106: 194.
<https://www.ncbi.nlm.nih.gov/pubmed/19922545>
714. Cespedes, R.D., *et al.* Long-term followup of incontinence and obstruction after salvage cryosurgical ablation of the prostate: results in 143 patients. *J Urol*, 1997. 157: 237.
<https://www.ncbi.nlm.nih.gov/pubmed/8976261>
715. Mouraviev, V., *et al.* Salvage cryoablation for locally recurrent prostate cancer following primary radiotherapy. *Eur Urol*, 2012. 61: 1204.
<https://www.ncbi.nlm.nih.gov/pubmed/22421081>
716. Pisters, L.L., *et al.* The efficacy and complications of salvage cryotherapy of the prostate. *J Urol*, 1997. 157: 921.
<https://www.ncbi.nlm.nih.gov/pubmed/9072600>
717. Ahmad, I., *et al.* Prostate gland lengths and iceball dimensions predict micturition functional outcome following salvage prostate cryotherapy in men with radiation recurrent prostate cancer. *PLoS One*, 2013. 8: e69243.
<https://www.ncbi.nlm.nih.gov/pubmed/23950886>
718. Chen, C.P., *et al.* Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes. *Int J Radiat Oncol Biol Phys*, 2013. 86: 324.
<https://www.ncbi.nlm.nih.gov/pubmed/23474112>
719. Burri, R.J., *et al.* Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*, 2010. 77: 1338.
<https://www.ncbi.nlm.nih.gov/pubmed/20138442>
720. Gomez-Veiga, F., *et al.* Brachytherapy for the treatment of recurrent prostate cancer after radiotherapy or radical prostatectomy. *BJU Int*, 2012. 109 Suppl 1: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/22239225>
721. Yamada, Y., *et al.* A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. *Brachytherapy*, 2014. 13: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/24373762>
722. Lee, B., *et al.* Feasibility of high-dose-rate brachytherapy salvage for local prostate cancer recurrence after radiotherapy: the University of California-San Francisco experience. *Int J Radiat Oncol Biol Phys*, 2007. 67: 1106.
<https://www.ncbi.nlm.nih.gov/pubmed/17197119>
723. Moman, M.R., *et al.* Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. *Brachytherapy*, 2010. 9: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/19850536>
724. Colombel M, P.L., Martin X, *et al.* Clinical results of the prostate HIFU project. *Eur Urol Suppl*, 2006: 491.
[http://www.europeanurology.com/article/S1569-9056\(06\)00023-6/abstract/clinical-results-of-the-prostate-hifu-project](http://www.europeanurology.com/article/S1569-9056(06)00023-6/abstract/clinical-results-of-the-prostate-hifu-project)
725. Gelet, A., *et al.* Transrectal high-intensity focused ultrasound: minimally invasive therapy of localized prostate cancer. *J Endourol*, 2000. 14: 519.
<https://www.ncbi.nlm.nih.gov/pubmed/>
726. Gelet, A., *et al.* Local recurrence of prostate cancer after external beam radiotherapy: early experience of salvage therapy using high-intensity focused ultrasonography. *Urology*, 2004. 63: 625.
<https://www.ncbi.nlm.nih.gov/pubmed/10037389>

727. Uchida, T., *et al.* High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after external beam radiation, brachytherapy or proton therapy. *BJU Int*, 2011. 107: 378.
<https://www.ncbi.nlm.nih.gov/pubmed/21265984>
728. Berge, V., *et al.* Health-related quality of life after salvage high-intensity focused ultrasound (HIFU) treatment for locally radiorecurrent prostate cancer. *Int J Urol*, 2011. 18: 646.
<https://www.ncbi.nlm.nih.gov/pubmed/21771102>
729. Pinover, W.H., *et al.* Validation of a treatment policy for patients with prostate specific antigen failure after three-dimensional conformal prostate radiation therapy. *Cancer*, 2003. 97: 1127.
<https://www.ncbi.nlm.nih.gov/pubmed/12569615>
730. Karnes, R.J., *et al.* Salvage lymph node dissection for prostate cancer nodal recurrence detected by ¹¹C-choline positron emission tomography/computerized tomography. *J Urol*, 2015. 193: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/25150640>
731. Suardi, N., *et al.* Long-term outcomes of salvage lymph node dissection for clinically recurrent prostate cancer: results of a single-institution series with a minimum follow-up of 5 years. *Eur Urol*, 2015. 67: 299.
<https://www.ncbi.nlm.nih.gov/pubmed/24571959>
732. Tilki, D., *et al.* Salvage lymph node dissection for nodal recurrence of prostate cancer after radical prostatectomy. *J Urol*, 2015. 193: 484.
<https://www.ncbi.nlm.nih.gov/pubmed/25180792>
733. Rigatti, P., *et al.* Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by [¹¹C]choline positron emission tomography/computed tomography. *Eur Urol*, 2011. 60: 935.
<https://www.ncbi.nlm.nih.gov/pubmed/21840116>
734. Rischke, H.C., *et al.* Adjuvant radiotherapy after salvage lymph node dissection because of nodal relapse of prostate cancer versus salvage lymph node dissection only. *Strahlenther Onkol*, 2015. 191: 310.
<https://www.ncbi.nlm.nih.gov/pubmed/25326142>
735. Ploussard, G., *et al.* Management of Node Only Recurrence after Primary Local Treatment for Prostate Cancer: A Systematic Review of the Literature. *J Urol*, 2015. 194: 983.
<https://www.ncbi.nlm.nih.gov/pubmed/25963190>
736. Eisenhauer, E.A., *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, 2009. 45: 228.
<https://www.ncbi.nlm.nih.gov/pubmed/19097774>
737. Smith, M.R., *et al.* Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol*, 2005. 23: 2918.
<https://www.ncbi.nlm.nih.gov/pubmed/15860850>
738. Smith, M.R., *et al.* Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. *Cancer*, 2011. 117: 2077.
<https://www.ncbi.nlm.nih.gov/pubmed/21523719>
739. Crawford, E.D., *et al.* Challenges and recommendations for early identification of metastatic disease in prostate cancer. *Urology*, 2014. 83: 664.
<https://www.ncbi.nlm.nih.gov/pubmed/24411213>
740. Hussain, M., *et al.* Effects of continued androgen-deprivation therapy and other prognostic factors on response and survival in phase II chemotherapy trials for hormone-refractory prostate cancer: a Southwest Oncology Group report. *J Clin Oncol*, 1994. 12: 1868.
<https://www.ncbi.nlm.nih.gov/pubmed/8083710>
741. Taylor, C.D., *et al.* Importance of continued testicular suppression in hormone-refractory prostate cancer. *J Clin Oncol*, 1993. 11: 2167.
<https://www.ncbi.nlm.nih.gov/pubmed/8229130>
742. Scher, H.I., *et al.* Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*, 2008. 26: 1148.
<https://www.ncbi.nlm.nih.gov/pubmed/18309951>
743. Tannock, I.F., *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*, 2004. 351: 1502.
<https://www.ncbi.nlm.nih.gov/pubmed/15470213>

744. Ryan, C.J., *et al.* Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*, 2013. 368: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/23228172>
745. Rathkopf, D.E., *et al.* Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol*, 2014. 66: 815.
<https://www.ncbi.nlm.nih.gov/pubmed/24647231>
746. Ryan, C.J., *et al.* Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*, 2015. 16: 152.
<https://www.ncbi.nlm.nih.gov/pubmed/23228172>
747. Beer, T.M., *et al.* Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*, 2014. 371: 424.
<https://www.ncbi.nlm.nih.gov/pubmed/24881730>
748. Kantoff, P.W., *et al.* Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol*, 2010. 28: 1099.
<https://www.ncbi.nlm.nih.gov/pubmed/20100959>
749. Small, E.J., *et al.* Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol*, 2006. 24: 3089.
<https://www.ncbi.nlm.nih.gov/pubmed/16809734>
750. Smith, M.R., *et al.* Efficacy and Safety of Abiraterone Acetate in Elderly (75 Years or Older) Chemotherapy Naive Patients with Metastatic Castration Resistant Prostate Cancer. *J Urol*, 2015. 194: 1277.
<https://www.ncbi.nlm.nih.gov/pubmed/26151676>
751. Graff, J.N., *et al.* Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castration-resistant prostate cancer: results from PREVAIL. *Ann Oncol*, 2016. 27: 286.
<https://www.ncbi.nlm.nih.gov/pubmed/26578735>
752. Evans, C.P., *et al.* The PREVAIL Study: Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-treated Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer. *Eur Urol*, 2016. 70: 675.
<https://www.ncbi.nlm.nih.gov/pubmed/27006332>
753. Shore, N.D., *et al.* Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *Lancet Oncol*, 2016. 17: 153.
<https://www.ncbi.nlm.nih.gov/pubmed/26774508>
754. Eisenberger M, *et al.* Multivariate prognostic nomogram incorporating PSA kinetics in hormone-refractory metastatic prostate cancer (HRPC). Abstract. ASCO Annual Meeting Proceedings (Post-Meeting Edition). *J Clin Oncol* 2007. 25: #5058.
http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.5058
755. Armstrong, A.J., *et al.* Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. *Clin Cancer Res*, 2010. 16: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/20008841>
756. Horgan, A.M., *et al.* Tolerability and efficacy of docetaxel in older men with metastatic castrate-resistant prostate cancer (mCRPC) in the TAX 327 trial. *J Geriatr Oncol*, 2014. 5: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/24495703>
757. Kellokumpu-Lehtinen, P.L., *et al.* 2-Weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. *Lancet Oncol*, 2013. 14: 117.
<https://www.ncbi.nlm.nih.gov/pubmed/23294853>
758. Parker, C., *et al.* Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*, 2013. 369: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/23863050>
759. Scher, H.I., *et al.* Clinical trials in relapsed prostate cancer: defining the target. *J Natl Cancer Inst*, 1996. 88: 1623.
<https://www.ncbi.nlm.nih.gov/pubmed/8931606>

760. Sartor, A., *et al.* Cabazitaxel vs docetaxel in chemotherapy-naive (CN) patients with metastatic castration-resistant prostate cancer (mCRPC): A three-arm phase III study (FIRSTANA). *J Clin Oncol* 2016. 34: Abstract 5006.
<http://meetinglibrary.asco.org/content/166318-176>
761. de Bono, J.S., *et al.* Phase III non-inferiority study of cabazitaxel (C) 20 mg/m² (C20) versus 25 mg/m² (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D). *J Clin Oncol* 2016. 34: abstr 5008.
<http://meetinglibrary.asco.org/content/169889-176>
762. Resnick, M.J., *et al.* Prostate cancer survivorship care guideline: American Society of Clinical Oncology Clinical Practice Guideline endorsement. *J Clin Oncol*, 2015. 33: 1078.
<https://www.ncbi.nlm.nih.gov/pubmed/25667275>
763. Hoskin, P., *et al.* Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol*, 2014. 15: 1397.
<https://www.ncbi.nlm.nih.gov/pubmed/25439694>
764. Mateo, J., *et al.* DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med*, 2015. 373: 1697.
<https://www.ncbi.nlm.nih.gov/pubmed/26510020>
765. Badrising, S., *et al.* Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer*, 2014. 120: 968.
<https://www.ncbi.nlm.nih.gov/pubmed/24382803>
766. Zhang, T., *et al.* Enzalutamide versus abiraterone acetate for the treatment of men with metastatic castration-resistant prostate cancer. *Expert Opin Pharmacother*, 2015. 16: 473.
<https://www.ncbi.nlm.nih.gov/pubmed/25534660>
767. Antonarakis, E.S., *et al.* AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med*, 2014. 371: 1028.
<https://www.ncbi.nlm.nih.gov/pubmed/25184630>
768. Gillesen, S., *et al.* Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. *Ann Oncol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27141017>
769. Payne, H., *et al.* Prostate-specific antigen: an evolving role in diagnosis, monitoring, and treatment evaluation in prostate cancer. *Urol Oncol*, 2011. 29: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/20060331>
770. Pezaro, C.J., *et al.* Visceral disease in castration-resistant prostate cancer. *Eur Urol*, 2014. 65: 270.
<https://www.ncbi.nlm.nih.gov/pubmed/24295792>
771. Ohlmann C, *et al.* Second-line chemotherapy with docetaxel for prostate-specific antigen relapse in men with hormone refractory prostate cancer previously treated with docetaxel based chemotherapy. *Eur Urol Suppl* 2006. 5: abstract #289.
http://ascopubs.org/doi/abs/10.1200/jco.2005.23.16_suppl.4682
772. Esper, P.S., *et al.* Supportive care in the patient with hormone refractory prostate cancer. *Semin Urol Oncol*, 1997. 15: 56.
<https://www.ncbi.nlm.nih.gov/pubmed/9050140>
773. Dy, S.M., *et al.* Evidence-based standards for cancer pain management. *J Clin Oncol*, 2008. 26: 3879.
<https://www.ncbi.nlm.nih.gov/pubmed/18688056>
774. Hartsell, W.F., *et al.* Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst*, 2005. 97: 798.
<https://www.ncbi.nlm.nih.gov/pubmed/15928300>
775. Hoskin, P., *et al.* A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. *J Natl Cancer Inst*, 2015. 107.
<https://www.ncbi.nlm.nih.gov/pubmed/26242893>
776. Frankel, B.M., *et al.* Percutaneous vertebral augmentation: an elevation in adjacent-level fracture risk in kyphoplasty as compared with vertebroplasty. *Spine J*, 2007. 7: 575.
<https://www.ncbi.nlm.nih.gov/pubmed/17905320>
777. Dutka, J., *et al.* Time of survival and quality of life of the patients operatively treated due to pathological fractures due to bone metastases. *Ortop Traumatol Rehabil*, 2003. 5: 276.
<https://www.ncbi.nlm.nih.gov/pubmed/18034018>

778. Frankel, B.M., *et al.* Segmental polymethylmethacrylate-augmented pedicle screw fixation in patients with bone softening caused by osteoporosis and metastatic tumor involvement: a clinical evaluation. *Neurosurgery*, 2007. 61: 531.
<https://www.ncbi.nlm.nih.gov/pubmed/17881965>
779. Marco, R.A., *et al.* Functional and oncological outcome of acetabular reconstruction for the treatment of metastatic disease. *J Bone Joint Surg Am*, 2000. 82: 642.
<https://www.ncbi.nlm.nih.gov/pubmed/10819275>
780. Saad, F., *et al.* A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*, 2002. 94: 1458.
<https://www.ncbi.nlm.nih.gov/pubmed/12359855>
781. Fizazi, K., *et al.* Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*, 2011. 377: 813.
<https://www.ncbi.nlm.nih.gov/pubmed/21353695>
782. Smith, M.R., *et al.* Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*, 2012. 379: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/22093187>
783. Aapro, M., *et al.* Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol*, 2008. 19: 420.
<https://www.ncbi.nlm.nih.gov/pubmed/17906299>
784. Horwitz, E.M., *et al.* Definitions of biochemical failure that best predict clinical failure in patients with prostate cancer treated with external beam radiation alone: a multi-institutional pooled analysis. *J Urol*, 2005. 173: 797.
<https://www.ncbi.nlm.nih.gov/pubmed/15711272>
785. Stephenson, A.J., *et al.* Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. *J Clin Oncol*, 2006. 24: 3973.
<https://www.ncbi.nlm.nih.gov/pubmed/16921049>
786. Boccon-Gibod, L., *et al.* Management of prostate-specific antigen relapse in prostate cancer: a European Consensus. *Int J Clin Pract*, 2004. 58: 382.
<https://www.ncbi.nlm.nih.gov/pubmed/15161124>
787. Shen, S., *et al.* Ultrasensitive serum prostate specific antigen nadir accurately predicts the risk of early relapse after radical prostatectomy. *J Urol*, 2005. 173: 777.
<https://www.ncbi.nlm.nih.gov/pubmed/15711268>
788. Eisenberg, M.L., *et al.* Prognostic implications of an undetectable ultrasensitive prostate-specific antigen level after radical prostatectomy. *Eur Urol*, 2010. 57: 622.
<https://www.ncbi.nlm.nih.gov/pubmed/19375843>
779. Stamey, T.A., *et al.* Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. *J Urol*, 1989. 141: 1076.
<https://www.ncbi.nlm.nih.gov/pubmed/2468795>
790. Partin, A.W., *et al.* Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. *Urology*, 1994. 43: 649.
<https://www.ncbi.nlm.nih.gov/pubmed/7513108>
791. Oefelein, M.G., *et al.* The incidence of prostate cancer progression with undetectable serum prostate specific antigen in a series of 394 radical prostatectomies. *J Urol*, 1995. 154: 2128.
<https://www.ncbi.nlm.nih.gov/pubmed/7500474>
792. Ray, M.E., *et al.* PSA nadir predicts biochemical and distant failures after external beam radiotherapy for prostate cancer: a multi-institutional analysis. *Int J Radiat Oncol Biol Phys*, 2006. 64: 1140.
<https://www.ncbi.nlm.nih.gov/pubmed/16198506>
793. Hancock, S.L., *et al.* Prostate specific antigen after radiotherapy for prostate cancer: a reevaluation of long-term biochemical control and the kinetics of recurrence in patients treated at Stanford University. *J Urol*, 1995. 154: 1412.
<https://www.ncbi.nlm.nih.gov/pubmed/7544843>
794. Chaplin, B.J., *et al.* Digital rectal examination is no longer necessary in the routine follow-up of men with undetectable prostate specific antigen after radical prostatectomy: the implications for follow-up. *Eur Urol*, 2005. 48: 906.
<https://www.ncbi.nlm.nih.gov/pubmed/16126322>
795. Collette, L., *et al.* Prostate specific antigen: a prognostic marker of survival in good prognosis metastatic prostate cancer? (EORTC 30892). *Eur Urol*, 2003. 44: 182.
<https://www.ncbi.nlm.nih.gov/pubmed/12875936>

796. Stewart, A.J., *et al.* Prostate-specific antigen nadir and cancer-specific mortality following hormonal therapy for prostate-specific antigen failure. *J Clin Oncol*, 2005. 23: 6556.
<https://www.ncbi.nlm.nih.gov/pubmed/16170163>
797. Beer, T.M., *et al.* The prognostic value of hemoglobin change after initiating androgen-deprivation therapy for newly diagnosed metastatic prostate cancer: A multivariate analysis of Southwest Oncology Group Study 8894. *Cancer*, 2006. 107: 489.
<https://www.ncbi.nlm.nih.gov/pubmed/16804926>
798. Daniell, H.W. Osteoporosis due to androgen deprivation therapy in men with prostate cancer. *Urology*, 2001. 58: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/11502461>
799. Miller, P.D., *et al.* Prostate specific antigen and bone scan correlation in the staging and monitoring of patients with prostatic cancer. *Br J Urol*, 1992. 70: 295.
<https://www.ncbi.nlm.nih.gov/pubmed/1384920>
800. Conde, F.A., *et al.* Risk factors for male osteoporosis. *Urol Oncol*, 2003. 21: 380.
<https://www.ncbi.nlm.nih.gov/pubmed/14670549>
801. Hamdy, R.C., *et al.* Algorithm for the management of osteoporosis. *South Med J*, 2010. 103: 1009.
<https://www.ncbi.nlm.nih.gov/pubmed/20818296>
802. Higano, C.S. Bone loss and the evolving role of bisphosphonate therapy in prostate cancer. *Urol Oncol*, 2003. 21: 392.
<https://www.ncbi.nlm.nih.gov/pubmed/14670551>
803. Bourke, L., *et al.* Survivorship and Improving Quality of Life in Men with Prostate Cancer. *Eur Urol* 68(3):374-83., 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25941049>
804. Burkhard, F.C., *et al.* The role of lymphadenectomy in prostate cancer. *Nat Clin Pract Urol*, 2005. 2: 336.
<https://www.ncbi.nlm.nih.gov/pubmed/16474786>
805. Ploussard, G., *et al.* Pelvic lymph node dissection during robot-assisted radical prostatectomy: efficacy, limitations, and complications-a systematic review of the literature. *Eur Urol*, 2014. 65: 7.
<https://www.ncbi.nlm.nih.gov/pubmed/23582879>
806. Davis, J.W., *et al.* Robot-assisted extended pelvic lymph node dissection (PLND) at the time of radical prostatectomy (RP): a video-based illustration of technique, results, and unmet patient selection needs. *BJU Int*, 2011. 108: 993.
<https://www.ncbi.nlm.nih.gov/pubmed/21917102>
807. Briganti, A., *et al.* Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. *Eur Urol*, 2006. 50: 1006.
<https://www.ncbi.nlm.nih.gov/pubmed/16959399>
808. Fowler, F.J., Jr., *et al.* Outcomes of external-beam radiation therapy for prostate cancer: a study of Medicare beneficiaries in three surveillance, epidemiology, and end results areas. *J Clin Oncol*, 1996. 14: 2258.
<https://www.ncbi.nlm.nih.gov/pubmed/8708715>
809. Robinson, J.W., *et al.* Meta-analysis of rates of erectile function after treatment of localized prostate carcinoma. *Int J Radiat Oncol Biol Phys*, 2002. 54: 1063.
<https://www.ncbi.nlm.nih.gov/pubmed/12419432>
810. Baxter, N.N., *et al.* Increased risk of rectal cancer after prostate radiation: a population-based study. *Gastroenterology*, 2005. 128: 819.
<https://www.ncbi.nlm.nih.gov/pubmed/15825064>
811. Liauw, S.L., *et al.* Second malignancies after prostate brachytherapy: incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. *Int J Radiat Oncol Biol Phys*, 2006. 66: 669.
<https://www.ncbi.nlm.nih.gov/pubmed/16887293>
812. Abdel-Wahab, M., *et al.* Second primary cancer after radiotherapy for prostate cancer--a seer analysis of brachytherapy versus external beam radiotherapy. *Int J Radiat Oncol Biol Phys*, 2008. 72: 58.
<https://www.ncbi.nlm.nih.gov/pubmed/18374503>
813. Zelefsky, M.J., *et al.* Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*, 2008. 70: 1124.
<https://www.ncbi.nlm.nih.gov/pubmed/18313526>

814. Budaus, L., *et al.* Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. *Eur Urol*, 2012. 61: 112.
<https://www.ncbi.nlm.nih.gov/pubmed/22001105>
815. Elshaiikh, M.A., *et al.* Prophylactic tamsulosin (Flomax) in patients undergoing prostate 125I brachytherapy for prostate carcinoma: final report of a double-blind placebo-controlled randomized study. *Int J Radiat Oncol Biol Phys*, 2005. 62: 164.
<https://www.ncbi.nlm.nih.gov/pubmed/15850917>
816. Reed, D.R., *et al.* A prospective randomized comparison of stranded vs. loose 125I seeds for prostate brachytherapy. *Brachytherapy*, 2007. 6: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/17434106>
817. Huang, E.H., *et al.* Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*, 2002. 54: 1314.
<https://www.ncbi.nlm.nih.gov/pubmed/12459352>
818. Moinpour, C.M., *et al.* Quality of life in advanced prostate cancer: results of a randomized therapeutic trial. *J Natl Cancer Inst*, 1998. 90: 1537.
<https://www.ncbi.nlm.nih.gov/pubmed/9790546>
819. Cherrier, M.M., *et al.* Cognitive and mood changes in men undergoing intermittent combined androgen blockade for non-metastatic prostate cancer. *Psychooncology*, 2009. 18: 237.
<https://www.ncbi.nlm.nih.gov/pubmed/18636420>
820. Herr, H.W., *et al.* Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. *J Urol*, 2000. 163: 1743.
<https://www.ncbi.nlm.nih.gov/pubmed/10799173>
821. Potosky, A.L., *et al.* Quality-of-life outcomes after primary androgen deprivation therapy: results from the Prostate Cancer Outcomes Study. *J Clin Oncol*, 2001. 19: 3750.
<https://www.ncbi.nlm.nih.gov/pubmed/11533098>
822. Iversen, P., *et al.* Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. *J Urol*, 2000. 164: 1579.
<https://www.ncbi.nlm.nih.gov/pubmed/11025708>
823. Iversen, P., *et al.* Nonsteroidal antiandrogens: a therapeutic option for patients with advanced prostate cancer who wish to retain sexual interest and function. *BJU Int*, 2001. 87: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/11121992>
824. Boccardo, F., *et al.* Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: results of an Italian Prostate Cancer Project study. *J Clin Oncol*, 1999. 17: 2027.
<https://www.ncbi.nlm.nih.gov/pubmed/10561254>
825. Elliott, S., *et al.* Androgen deprivation therapy for prostate cancer: recommendations to improve patient and partner quality of life. *J Sex Med*, 2010. 7: 2996.
<https://www.ncbi.nlm.nih.gov/pubmed/20626600>
826. Sakai, H., *et al.* Hot flashes during androgen deprivation therapy with luteinizing hormone-releasing hormone agonist combined with steroidal or nonsteroidal antiandrogen for prostate cancer. *Urology*, 2009. 73: 635.
<https://www.ncbi.nlm.nih.gov/pubmed/19038426>
827. Irani, J., *et al.* Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flashes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol*, 2010. 11: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/19963436>
828. Sloan, J.A., *et al.* Methodologic lessons learned from hot flash studies. *J Clin Oncol*, 2001. 19: 4280.
<https://www.ncbi.nlm.nih.gov/pubmed/11731510>
829. Moraska, A.R., *et al.* Gabapentin for the management of hot flashes in prostate cancer survivors: a longitudinal continuation Study-NCCTG Trial N00CB. *J Support Oncol*, 2010. 8: 128.
<https://www.ncbi.nlm.nih.gov/pubmed/20552926>
830. Frisk, J., *et al.* Two modes of acupuncture as a treatment for hot flashes in men with prostate cancer--a prospective multicenter study with long-term follow-up. *Eur Urol*, 2009. 55: 156.
<https://www.ncbi.nlm.nih.gov/pubmed/18294761>
831. Smith, M.R., *et al.* Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. *J Urol*, 2006. 175: 136.
<https://www.ncbi.nlm.nih.gov/pubmed/16406890>
832. Cree, M., *et al.* Mortality and institutionalization following hip fracture. *J Am Geriatr Soc*, 2000. 48: 283.
<https://www.ncbi.nlm.nih.gov/pubmed/10733054>

833. Saylor, P.J., *et al.* Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol*, 2009. 181: 1998.
<https://www.ncbi.nlm.nih.gov/pubmed/19286225>
834. Sieber, P.R., *et al.* Bicalutamide 150 mg maintains bone mineral density during monotherapy for localized or locally advanced prostate cancer. *J Urol*, 2004. 171: 2272.
<https://www.ncbi.nlm.nih.gov/pubmed/15126801>
835. Wadhwa, V.K., *et al.* Bicalutamide monotherapy preserves bone mineral density, muscle strength and has significant health-related quality of life benefits for osteoporotic men with prostate cancer. *BJU Int*, 2011. 107: 1923.
<https://www.ncbi.nlm.nih.gov/pubmed/20950306>
836. Smith, M.R., *et al.* Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol*, 2003. 169: 2008.
<https://www.ncbi.nlm.nih.gov/pubmed/12771706>
837. Michaelson, M.D., *et al.* Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. *J Clin Oncol*, 2007. 25: 1038.
<https://www.ncbi.nlm.nih.gov/pubmed/17369566>
838. Migliorati, C.A., *et al.* Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *Lancet Oncol*, 2006. 7: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/16750501>
839. Wadhwa, V.K., *et al.* Frequency of zoledronic acid to prevent further bone loss in osteoporotic patients undergoing androgen deprivation therapy for prostate cancer. *BJU Int*, 2010. 105: 1082.
<https://www.ncbi.nlm.nih.gov/pubmed/19912210>
840. Dearnaley, D.P., *et al.* Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. *Lancet Oncol*, 2009. 10: 872.
<https://www.ncbi.nlm.nih.gov/pubmed/19674936>
841. Smith, M.R., *et al.* Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med*, 2009. 361: 745.
<https://www.ncbi.nlm.nih.gov/pubmed/19671656>
844. Nobes, J.P., *et al.* A prospective, randomized pilot study evaluating the effects of metformin and lifestyle intervention on patients with prostate cancer receiving androgen deprivation therapy. *BJU Int*, 2012. 109: 1495.
<https://www.ncbi.nlm.nih.gov/pubmed/21933330>
843. Grundy, S.M., *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*, 2005. 112: 2735.
<https://www.ncbi.nlm.nih.gov/pubmed/16157765>
844. Braga-Basaria, M., *et al.* Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol*, 2006. 24: 3979.
<https://www.ncbi.nlm.nih.gov/pubmed/16921050>
845. Lu-Yao, G., *et al.* Changing patterns in competing causes of death in men with prostate cancer: a population based study. *J Urol*, 2004. 171: 2285.
<https://www.ncbi.nlm.nih.gov/pubmed/15126804>
846. Keating, N.L., *et al.* Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst*, 2010. 102: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/19996060>
847. Efsthathiou, J.A., *et al.* Cardiovascular mortality and duration of androgen deprivation for locally advanced prostate cancer: analysis of RTOG 92-02. *Eur Urol*, 2008. 54: 816.
<https://www.ncbi.nlm.nih.gov/pubmed/18243498>
848. Nguyen, P.L., *et al.* Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. *Jama*, 2011. 306: 2359.
<https://www.ncbi.nlm.nih.gov/pubmed/22147380>
849. Nguyen, P.L., *et al.* Influence of androgen deprivation therapy on all-cause mortality in men with high-risk prostate cancer and a history of congestive heart failure or myocardial infarction. *Int J Radiat Oncol Biol Phys*, 2012. 82: 1411.
<https://www.ncbi.nlm.nih.gov/pubmed/21708431>
850. Tsai, H.K., *et al.* Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst*, 2007. 99: 1516.
<https://www.ncbi.nlm.nih.gov/pubmed/17925537>

851. Albertsen, P.C., *et al.* Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur Urol*, 2014. 65: 565.
<https://www.ncbi.nlm.nih.gov/pubmed/24210090>
852. Galvao, D.A., *et al.* Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*, 2010. 28: 340.
<https://www.ncbi.nlm.nih.gov/pubmed/19949016>
853. Culos-Reed, S.N., *et al.* Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention. *Support Care Cancer*, 2010. 18: 591.
<https://www.ncbi.nlm.nih.gov/pubmed/19609570>
854. Cormie, P., *et al.* Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: longitudinal results of a pilot study. *Support Care Cancer*, 2014. 22: 1537.
<https://www.ncbi.nlm.nih.gov/pubmed/24424484>
855. Kenfield, S.A., *et al.* Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol*, 2011. 29: 726.
<https://www.ncbi.nlm.nih.gov/pubmed/21205749>
856. Ahmadi, H., *et al.* Androgen deprivation therapy: evidence-based management of side effects. *BJU Int*, 2013. 111: 543.
<https://www.ncbi.nlm.nih.gov/pubmed/23351025>
857. Meng, F., *et al.* Stroke related to androgen deprivation therapy for prostate cancer: a meta-analysis and systematic review. *BMC Cancer*, 2016. 16: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/26940836>
858. Nead, K.T., *et al.* Androgen Deprivation Therapy and Future Alzheimer's Disease Risk. *J Clin Oncol*, 2016. 34: 566.
<https://www.ncbi.nlm.nih.gov/pubmed/26644522>
859. King, A.J., *et al.* Prostate cancer and supportive care: a systematic review and qualitative synthesis of men's experiences and unmet needs. *Eur J Cancer Care (Engl)*, 2015. 24: 618.
<https://www.ncbi.nlm.nih.gov/pubmed/25630851>
860. Bourke, L., *et al.* A qualitative study evaluating experiences of a lifestyle intervention in men with prostate cancer undergoing androgen suppression therapy. *Trials*, 2012. 13: 208.
<https://www.ncbi.nlm.nih.gov/pubmed/23151126>
861. Nguyen, P.L., *et al.* Adverse Effects of Androgen Deprivation Therapy and Strategies to Mitigate Them. *Eur Urol*, 2014: 67(5):825.
<https://www.ncbi.nlm.nih.gov/pubmed/25097095>
862. Berruti, A., *et al.* Incidence of skeletal complications in patients with bone metastatic prostate cancer and hormone refractory disease: predictive role of bone resorption and formation markers evaluated at baseline. *J Urol*, 2000. 164: 1248.
<https://www.ncbi.nlm.nih.gov/pubmed/10992374>
863. Carlin, B.I., *et al.* The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer*, 2000. 88: 2989.
<https://www.ncbi.nlm.nih.gov/pubmed/10898342>
864. Smith, D.P., *et al.* Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. *BMJ*, 2009. 339: b4817.
<https://www.ncbi.nlm.nih.gov/pubmed/19945997>
865. Taylor, K.L., *et al.* Long-term disease-specific functioning among prostate cancer survivors and noncancer controls in the prostate, lung, colorectal, and ovarian cancer screening trial. *J Clin Oncol*, 2012. 30: 2768.
<https://www.ncbi.nlm.nih.gov/pubmed/22734029>
866. Cella, D.F., *et al.* The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*, 1993. 11: 570.
<https://www.ncbi.nlm.nih.gov/pubmed/8445433>
867. Esper, P., *et al.* Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology*, 1997. 50: 920.
<https://www.ncbi.nlm.nih.gov/pubmed/9426724>
868. Groenvold, M., *et al.* Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J Clin Epidemiol*, 1997. 50: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/9179103>

869. van Andel, G., *et al.* An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. *Eur J Cancer*, 2008. 44: 2418.
<https://www.ncbi.nlm.nih.gov/pubmed/18774706>
870. Wei, J.T., *et al.* Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology*, 2000. 56: 899.
<https://www.ncbi.nlm.nih.gov/pubmed/11113727>
871. Szymanski, K.M., *et al.* Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology*, 2010. 76: 1245.
<https://www.ncbi.nlm.nih.gov/pubmed/20350762>
872. Litwin, M.S., *et al.* The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. *Med Care*, 1998. 36: 1002.
<https://www.ncbi.nlm.nih.gov/pubmed/9674618>
873. Giesler, R.B., *et al.* Assessing quality of life in men with clinically localized prostate cancer: development of a new instrument for use in multiple settings. *Qual Life Res*, 2000. 9: 645.
<https://www.ncbi.nlm.nih.gov/pubmed/11236855>
874. Potosky, A.L., *et al.* Prostate cancer practice patterns and quality of life: the Prostate Cancer Outcomes Study. *J Natl Cancer Inst*, 1999. 91: 1719. [no abstract available]
<https://www.ncbi.nlm.nih.gov/pubmed/10528021>
875. Donovan, J.L., *et al.* Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med*, 2016. 375: 1425.
<https://www.ncbi.nlm.nih.gov/pubmed/27626365>
876. Resnick, M.J., *et al.* Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med*, 2013. 368: 436.
<https://www.ncbi.nlm.nih.gov/pubmed/23363497>
877. Giberti, C., *et al.* Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. *World J Urol*, 2009. 27: 607.
<https://www.ncbi.nlm.nih.gov/pubmed/19455340>
878. Giesler, R.B., *et al.* Improving the quality of life of patients with prostate carcinoma: a randomized trial testing the efficacy of a nurse-driven intervention. *Cancer*, 2005. 104: 752.
<https://www.ncbi.nlm.nih.gov/pubmed/15986401>
879. Hatzimouratidis, K., *et al.* EAU Guidelines on Male Sexual Dysfunction. Edn presented at the EAU Annual Congress, London, 2017.
880. Dieperink, K.B., *et al.* The effects of multidisciplinary rehabilitation: RePCa-a randomised study among primary prostate cancer patients. *Br J Cancer*, 2013. 109: 3005.
<https://www.ncbi.nlm.nih.gov/pubmed/24169342>
881. Bourke, L., *et al.* Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. *Eur Urol*, 2014. 65: 865.
<https://www.ncbi.nlm.nih.gov/pubmed/24119318>
882. Cella, D., *et al.* Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health*, 2009. 12: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/18647260>
883. Bourke, L., *et al.* Exercise for Men with Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*, 2015: 69(4):693.
<https://www.ncbi.nlm.nih.gov/pubmed/26632144>

10. CONFLICT OF INTEREST

All members of the EAU - ESTRO – ESUR – SIOG Prostate Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>.

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EAU Guidelines on Renal Cell Carcinoma

B. Ljungberg (Chair), L. Albiges, K. Bensalah,
A. Bex (Vice-chair), R.H. Giles (Patient Advocate), M. Hora,
M.A. Kuczyk, T. Lam, L. Marconi, A.S. Merseburger, T. Powles,
M. Staehler, A. Volpe
Guidelines Associates: S. Dabestani,
S. Fernández-Pello Montes, F. Hofmann, R. Tahbaz

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise and judgement when making treatment decisions for individual patients, but rather help to focus decisions whilst also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The RCC Guidelines Panel is an international group of clinicians consisting of urological surgeons, oncologists, methodologists, a pathologist and a radiologist, with particular expertise in the field of renal cancer care. Since 2015, the panel has incorporated a patient advocate to provide a consumer perspective for its guidelines.

All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/renal-cell-carcinoma/>.

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1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the RCC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU RCC Guidelines [1, 2]. All documents can be accessed on the EAU website: <http://uroweb.org/guideline/renal-cell-carcinoma/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU RCC Guidelines were first published in 2000. This 2017 RCC Guidelines document presents a limited update of the 2016 publication.

1.4.2 Summary of changes

All chapters of the 2017 RCC Guidelines have been updated, based on the 2016 version of the guideline. References have been added throughout the document.

Key changes in this 2017 print:

- Section 3.3.3 - Hereditary kidney tumours: This section has been expanded
- Section 5.2 - Imaging evaluations: The findings of a systematic review have been incorporated.

New data and recommendations have been included in the following sections:

5.4 Summary of evidence and recommendations for the diagnostic assessment of renal cell cancer

Summary of evidence	LE
Contrast enhanced multi-phasic CT has a high sensitivity and specificity for characterisation and detection of RCC, invasion, tumour thrombus and metastatic RCC.	2
MRI has a slightly higher sensitivity and specificity for small renal masses and tumour thrombus as compared to CT.	2
CEUS has a high sensitivity and specificity for characterisation of renal masses.	2
US, Power-Doppler US and PET-CT have a low sensitivity and specificity for detection and characterisation of RCC.	2

Recommendations	grade	
Use multi-phasic contrast-enhanced computed tomography (CT) for general staging and detection of renal cell cancer (RCC).	strong	↑↑
Use axial abdominal imaging and CT of the chest for staging of RCC.	strong	↑↑
Use non-ionising modalities, mainly contrast enhanced ultrasound (CEUS), for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	weak	↑
Do not use bone scan and/or positron-emission tomography (PET)-CT for staging of RCC.	weak	↓
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	strong	↑↑
Perform a percutaneous biopsy in select patients who are considered for active surveillance.	weak	↑
When performing a renal tumour biopsy technique, use a coaxial technique.	strong	↑↑
Do not perform a renal tumour biopsy of cystic renal masses.	weak	↓

7.2.5.1 Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b
Adjuvant sunitinib improved disease-free survival in one of the two available studies, but not overall survival, after nephrectomy in selected high-risk patients.	1b

Recommendations	grade	
Do not offer adjuvant therapy with sorafenib.	strong	↓↓
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell cancer.	weak	↓

7.3.2.5 Recommendations for local therapy of metastases in metastatic RCC

Recommendation	grade	
Consider local therapy for metastatic disease (including metastasectomy) in patients with a favourable risk profile in whom complete resection is achievable or when local symptoms need to be controlled.	weak	↑

7.4.1.1 Summary of evidence and recommendation for systemic therapy for advanced/metastatic renal cell cancer

Summary of evidence	LE
In metastatic RCC, 5-FU combined with immunotherapy has equivalent efficacy to INF- α .	1b
In metastatic RCC, chemotherapy is otherwise not effective with the exception of gemcitabine and doxorubicin in sarcomatoid and rapidly progressive disease.	3

Recommendations	grade	
Do not offer chemotherapy as first-line therapy in patients with metastatic clear-cell renal cell cancer (RCC).	strong	↓↓
Consider offering a combination of gemcitabine and doxorubicin to patients with sarcomatoid or rapidly progressive RCC.	weak	↑

7.4.6.3 Summary of evidence and recommendations for systemic therapy in metastatic renal cell cancer

Summary of evidence	LE
First line pazopanib is not inferior to sunitinib in clear-cell mRCC patients.	1b
Cabozantinib is superior to everolimus in terms of PFS and OS in patients failing one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy when compared to placebo.	1b
No combination has proven to be better than single-agent therapy, with the exception of the combination of lenvatinib plus everolimus.	1a

Recommendations	grade	
Offer sunitinib or pazopanib as first-line therapy for metastatic clear-cell renal cell cancer (ccRCC).	strong	↑↑
Consider offering bevacizumab + Interferon (IFN)-α as first-line therapy for metastatic RCC in favourable-risk and intermediate-risk ccRCC.	weak	↑
Consider offering temsirolimus as first-line treatment in poor-risk RCC patients.	weak	↑
Offer cabozantinib for ccRCC after one or two lines of vascular endothelial growth factor (VEGF)-targeted therapy in metastatic RCC.	strong	↑↑
Sunitinib can be offered as first-line therapy for non-clear cell mRCC.	weak	↑

2. METHODS

2.1 Data identification

For the 2017 Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature for the chapters as listed in Table 2.1.

A broad and comprehensive scoping exercise was performed. The search was limited to studies representing high levels of evidence (i.e. systematic reviews [SRs] with meta-analysis [MA], randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published between July 30th 2015 and June 30th 2016. Databases covered included Medline, EMBASE, and the Cochrane Library. A total of 1,602 unique records were identified, retrieved and screened for relevance. A search strategy is published online: <https://uroweb.org/guideline/renal-cell-carcinoma/?type=appendices-publications>.

Specific chapters were updated by way of SRs, commissioned and undertaken by the panel in conjunction with the EAU Guidelines Office, based on topics or questions prioritised by the Guidelines Panel. These reviews were performed using standard Cochrane SR methodology <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

The EAU Guidelines Office are in the process of introducing modified GRADE methodology across all 20 guidelines [3, 4]. This will be a phased introduction, with the RCC Guidelines Panel already incorporating these changes in their 2017 Guidelines print.

The Summary of Evidence (SOE) tables provided for each recommendation within the guidelines address a number of key elements:

1. the overall quality of the evidence which exists for the recommendation;
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' and is directional, either 'do it' (as represented by arrows pointing upwards) or 'do not do it' (arrows pointing downwards) [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The SOE tables will be posted online for consultation.

Table 2.1: Description of update and summary of review methodology

Chapter	Brief description of review methodology
1. Introduction	Not applicable
2. Methods	Not applicable
3. Epidemiology, aetiology and pathology	This chapter was updated by a traditional narrative review, based on a structured literature assessment.
4. Staging and grading classification systems	This chapter was updated by a traditional narrative review, based on a structured literature assessment.
5. Diagnostic evaluation	Section 5.2 (Diagnostic imaging) was revised based on a SR [6]. The remainder of the chapter was updated by a structured literature assessment.
6. Prognosis	This chapter was updated by a traditional narrative review, based on a structured literature assessment.
7. Treatment (Disease management)	Chapters 7.1.2 and 7.2.4 (Treatment of localised and locally advanced disease) were revised based on an updated SR. The remainder of the chapter was updated using a structured literature assessment. Systemic therapy for metastatic disease: this section was updated by a SR.
8. Surveillance following radical or partial nephrectomy or ablative therapies	This chapter was updated by a traditional narrative review, based on a structured literature assessment.

The findings of a number of SR topics have been incorporated in this 2017 update:

- Imaging in Suspected Renal Cell Carcinoma: A Systematic Review [6]
- What is the best surgical treatment option for clinical > T2, N0M0 tumours? What is the best way of performing this procedure? [7];
- A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma [8].

2.2 Review

Chapter 7 'Disease management' was peer reviewed prior to publication. Publications ensuing from SRs have all been peer reviewed. The other sections of the RCC Guidelines were peer reviewed prior to publication in 2015.

2.3 Future goals

For their future updates, the RCC Guideline Panel aims to focus on patient-reported outcomes.

The use of clinical quality indicators is an area of interest for the RCC Panel. A number of key quality indicators for this patient group have been selected:

- thorax computed tomography (CT) for staging of pulmonary metastasis;
- proportion of patients with T1aN0M0 tumours undergoing nephron-sparing surgery as first treatment;
- the proportion of patients treated within six weeks after diagnosis;
- the proportion of patients with metastatic RCC offered treatment with targeting agents;
- proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days;

Panel members have set up a database to capture current practice of follow-up of RCC patients in a number of European Centres. Assessing patterns of recurrence and use of imaging techniques are primary outcomes for this project.

The results of ongoing and new SRs will be included in the 2018 update of the RCC Guidelines.

Topics of ongoing SRs:

- What is the best treatment option for T1-T2 tumours? (updated review);
- What is the best treatment option for T1a tumours?;
- What is the best treatment option for T1b-T2a tumours? (updated review);
- What is the best treatment option for T2b tumours;
- Systematic review and meta-analysis of systemic therapy of renal tumours (Cochrane Review).

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell cancer represents 2-3% of all cancers [9], with the highest incidence in Western countries. Over the last two decades the incidence of RCC increased by about 2%, both worldwide and in Europe. In Western European countries this incidence stabilised over the past decade [10]. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney-cancer-related deaths in the European Union [11]. In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilised or declined thereafter [12]. Mortality has decreased since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend [12]. Data from the United States also show increased incidence [13].

There is a 1.5:1 male predominance, with a peak incidence between 60 and 70 years. Aetiological factors include smoking, obesity [14] and hypertension. Having a first-degree relative with RCC also increases the risk of RCC [15]. A number of other factors associated with higher or lower RCC-risk include specific dietary habits, occupational exposure to specific carcinogens, acetaminophen and non-aspirin non-steroidal anti-inflammatory drugs [16], cruciferous vegetables [17], nephrolithiasis [18], and viral hepatitis [19-23]. However, data from the literature are still inconclusive [24, 25]. Moderate alcohol consumption appears to have a protective effect for unknown reasons [26-28]. Effective prophylaxis includes avoidance of cigarette smoking and obesity.

Due to increased detection of tumours by ultrasound (US) and computed tomography (CT), the number of incidentally diagnosed RCCs has increased. These tumours are usually smaller and of lower stage [29-31].

3.1.1 Summary of evidence and recommendation

Summary of evidence	LE
Several verified risk factors have been identified including smoking, obesity and hypertension. These are considered definite risk factors for RCC.	2a

Recommendation	grade	
For the most important primary prevention of RCC, eliminate cigarette smoking and reduce weight.	strong	↑↑

3.2 Histological diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2016 World Health Organization (WHO) classification [32, 33]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC - type I and II) and chromophobe (chRCC). Renal cell cancer type classification has been confirmed by cytogenetic and genetic analyses [32, 33] (LE: 2b). Collecting duct carcinoma and other infrequent renal tumours are discussed in Section 3.3.

Histological diagnosis includes, besides RCC type; evaluation of nuclear grade, sarcomatoid features, vascular invasion, tumour necrosis, and invasion of the collecting system and peri-renal fat, pT or even pN categories. The four-tiered WHO/ISUP (International Society of Urological Pathology) grading system has replaced the Fuhrman grading system [32, 33].

3.2.1 Clear cell renal cell cancer

Overall, clear-cell RCC (ccRCC) is well circumscribed and a capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. Loss of chromosome 3p and mutation of the von Hippel-Lindau (VHL) gene at chromosome 3p25 are frequently found, including additional tumour suppressor genes including SETD2, BAP1, and PBRM1; all genes are identified near the VHL gene within a region that is frequently deleted in ccRCC [34]. In general, ccRCC has a worse prognosis compared to pRCC and chRCC [35, 36] even after stratification for stage and grade [37]. The five-year cancer-specific-survival (CSS) rate was 91%, 74%, 67% and 32% for TNM stages I, II, III and IV (patients treated between 1987-1998) [38]. For more details, see Section 6.3 - Histological factors.

3.2.2 **Papillary renal cell cancer**

Papillary RCC (pRCC) is the second most commonly encountered morphotype of RCC. Papillary RCC has traditionally been subdivided into two types [33]. Type 1 and 2 pRCC, which were shown to be clinically and biologically distinct; pRCC type 1 is associated with activating germline mutations of MET and pRCC type 2 is associated with activation of the NRF2-ARE pathway with at least three subtypes [39]. Macroscopically, pRCC is well circumscribed with pseudocapsule, yellow or brown in colour, and a soft structure. Compared to ccRCC, pRCC has a significantly higher rate of organ-confined tumour (pT1-2N0M0) and a higher five-year CSS rate [40]. Papillary RCC type 1 is more common and generally considered to have a better prognosis than pRCC type 2 [33, 41]. Exophytic spherical growth, pseudo-necrotic changes and pseudo-capsule are typical signs of pRCC type 1. Tumours are fragile. On post-contrast CT, a hypodense central area of tumour surrounded by vital tumour tissue is seen, presented as a serpiginous contrast-enhancing margin on CT [42].

3.2.3 **Chromophobe (chRCC)**

Overall, chRCC is a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Chromophobe RCC cannot be graded (by the Fuhrman grading system), because of its innate nuclear atypia. An alternative grading system has been proposed, but has yet to be validated [32, 33]. Loss of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [32, 33]. The prognosis is relatively good, with high five-year recurrence-free survival (RFS), and ten-year CSS [43]. The new WHO/ISUP Grading system merges former entity hybrid oncocytic chromophobe tumour with chRCC.

3.3 **Other renal tumours**

Other renal tumours constitute the remaining 10-15% of renal cortical tumours. These include a variety of uncommon, sporadic, and familial carcinomas, some only recently described, as well as a group of unclassified carcinomas. A summary of these tumours is provided in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below.

3.3.1 **Carcinoma associated with end-stage renal disease; acquired cystic disease-associated RCC**

Cystic degenerative changes (acquired cystic kidney disease [ACKD]) and a higher incidence of RCC are typical features of ESKD (end-stage kidney disease). Renal cell cancers of native end-stage kidneys are found in about 4% of patients. Their lifetime risk of developing RCCs is at least ten times higher than in the general population. Compared with sporadic RCCs, RCCs associated with ESKD are generally multicentric and bilateral, found in younger patients (mostly male), and are less aggressive [44, 45]. The relatively indolent outcome of tumours in ESKD is due to the mode of diagnosis and a specific ACKD-related molecular pathway which has still to be determined [45]. Although the histological spectrum of ESKD tumours is similar to that of sporadic RCC, the predominant form is pRCC. The remaining tumours are mostly ccRCC [44-46]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) [47] with indolent clinical behaviour, likely due to early detection in patients with ESKD on periodic follow-up [33].

3.3.2 **Papillary adenoma**

These tumours have a papillary or tubular architecture of low nuclear grade and may be up to 15 mm in diameter, or smaller [48], according to the WHO 2016 classification [33].

3.3.3 **Hereditary kidney tumours**

Five to eight percent of RCC is hereditary; to date there are ten hereditary RCC syndromes known, associated with specific germline mutations, RCC histology, and comorbidities. Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes. Median age for hereditary RCC is 37 years; 70% of hereditary RCC tumours are found in the lowest decile (≤ 46 years old) of all RCC tumours [49]. Hereditary kidney tumours are found in the following entities: VHL syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome (see Hybrid oncocytopoma-chromophobe carcinoma), hereditary leiomyomatosis and RCC (HLRCC), tuberous sclerosis (TS), germline succinate dehydrogenase (SDH) mutation, non-polyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS), constitutional chromosome 3 translocation, and familial nonsyndromic ccRCC. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [47, 48, 50, 51].

Patients with hereditary kidney cancer syndromes may require repeated surgical interventions [52, 53]. Appropriately timed nephron-sparing approaches are recommended with the exception of Hereditary Leiomyomatosis and RCC (HLRCC) and succinate dehydrogenase (SDH) syndromes, for which surveillance is recommended until the largest solid tumour reaches 3 cm in diameter, to reduce interventions [54]. Active

surveillance for VHL, BDH and HPRCC should, in individual patients, follow the growth kinetics, size and location of the tumours rather than apply a standardised fixed follow-up interval. Regular screening for both renal and extra-renal lesions should follow international guidelines for these syndromes. Multi-disciplinary and co-ordinated care should be offered, where appropriate [55].

Although not hereditary, somatic fusion translocations of TFE3 and TFEB may affect 15% of patients with RCC younger than 45 years and 20-45% of children and young adults with RCC [56].

3.3.4 **Angiomyolipoma**

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically, and is four times more common in females [57]. Angiomyolipoma also occurs in tuberous sclerosis and accounts for approximately 1% of surgically removed tumours. Ultrasound, CT, and magnetic resonance imaging (MRI) often lead to diagnosis due to the presence of adipose tissue. Biopsy is rarely useful. Pre-operatively, it may be difficult to differentiate between smooth muscle cell tumours and epithelial tumours. Angiomyolipoma can be found in tuberous sclerosis in lymph nodes (LNs), but it is not metastasis, and has a multicentric genesis. Angiomyolipoma can be due to angiotrophic-type growth extending into the renal vein or the inferior vena cava. Angiomyolipoma with LN involvement and tumorous thrombus is benign. Only epithelioid AML is potentially malignant [48, 58]. Angiomyolipoma has a slow and consistent growth rate, and minimal morbidity [59]. The main complications of renal AML are retroperitoneal bleeding or bleeding into the urinary collection system, which can be life-threatening [60]. The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels [60]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of tuberous sclerosis [60, 61]. Indications for intervention are pain, bleeding, or suspected malignancy.

3.3.4.1 *Treatment*

Active surveillance (AS) is the most appropriate option for most AMLs [57, 59, 62] (LE: 3). Risk factors for delayed intervention include tumour size > 4 cm and symptoms at diagnosis [62]. Selective arterial embolisation (SAE) seems to be the first-line option used for active treatment after AS is discontinued [62] (LE: 3). Selective arterial embolisation is an efficient treatment for AML devascularisation, but only for volume reduction [63].

Although SAE controls haemorrhage in the acute setting, it has limited value long-term [64, 65]. If surgery is selected, most cases of AML can be managed by conservative nephron-sparing surgery (NSS), although some patients may require complete nephrectomy [61] (LE: 3). Radiofrequency ablation (RFA) can be an option as well [59, 60, 66]. The volume of AML can be reduced by the mammalian target of rapamycin (mTOR) inhibitor everolimus [67]. A clinical phase II trial and its open-label extension of medical management with everolimus in AMLs not requiring surgical intervention, showed a response rate of 81.6 (64.5% (\geq 50% or 30% tumour volume reduction) by week 96, confirming the long-term safety profile of everolimus [67]. Sirolimus can be combined with deferred surgery [68].

Table 3.1: Other renal cortical tumours, and recommendations for treatment (grade: weak) [32, 33]

Entity	Clinical relevant notes	Malignant potential	Treatment of localised tumour/metastatic tumour
Sarcomatoid variants of RCC	Sign of high-grade transformation without being a distinct histological entity.	High	Surgery. Sunitinib, gemcitabine plus doxorubicin is also an option [69].
Multilocular cystic renal neoplasm of low malignant potential	Formerly multilocular cystic RCC	Benign	Surgery, nephron-sparing surgery (NSS).
Carcinoma of the collecting ducts of Bellini	Rare, often presenting at an advanced stage (N+ 44% and M1 33% at diagnosis). The hazard ratio (HR) CSS in comparison with ccRCC is 4.49 [36].	High, very aggressive. Median survival 30 months [70].	Surgery. Response to targeted therapies is poor [71].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is five months [70].	Surgery. Different chemotherapy regimes, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients < 40, more common in females. It constitutes with TRCC 6p21 MiT translocation RCCs [72].	High	Surgery. Vascular endothelial growth factor (VEGF)-targeted therapy.
Translocation RCC t(6;11)		Low/intermediate	Surgery, NSS. VEGF-targeted therapy.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle.	Intermediate	Surgery, NSS.
Acquired cystic disease-associated RCC		Low	Surgery.
Clear cell papillary RCC	Also reported as renal angiomyomatous tumour (RAT).	Low	Surgery, NSS.
Hereditary leiomyomatosis and RCC-associated RCC	Rare, new entity in the 2016 WHO classification, caused by a germline mutation of the fumarate hydratase gene [33].	Aggressive	Surgery. No data about treatment of metastatic disease.
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Succinate dehydrogenase-deficient RCC	Rare.	Low	Surgery.
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	Surgery, NSS.
Cystic nephroma/Mixed Epithelial and Stromal Tumour	Term renal epithelial and stromal tumours (REST) is used as well. Imaging – Bosniak type III or II/IV.	Low/benign	Surgery, NSS.
Oncocytoma	3-7% of all renal tumours. Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard [73, 74].	Benign	Observation (when histologically confirmed) [75-77]. NSS.

Hereditary kidney tumours	Details see above.	High	Surgery, NSS.
Angiomyolipoma	Details see above.	Benign	Consider treatment only in very well selected patients.
Unclassified RCC	RCC that cannot be assigned to any other category of RCC-type carcinoma [48].	Variable	Surgery, NSS.

3.3.4.2 Summary

A variety of renal tumours exist, and about 15% are benign. All kidney lesions require examination for malignant behaviour.

3.4 Summary of evidence and recommendations for the management of other renal tumours

Recommendations	grade	
Treat Bosniak type III or IV cysts the same as RCC.	strong	↑↑
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: <ul style="list-style-type: none"> large tumours (a recommended threshold of intervention does not exist, the formerly recommended size of > 4 cm wide is disputed); females of childbearing age; patients in whom follow-up or access to emergency care may be inadequate. 	weak	↑
Treat AMLs that are not candidates for active treatment with active surveillance.	weak	↑
In AML > 3 cm not requiring surgical intervention, medical treatment with everolimus can be considered.	weak	↑
Offer active surveillance to patients with biopsy-proven oncocytomas.	weak	↑
For advanced uncommon renal tumours, develop individualised oncological treatment plans for each patient.	strong	↑↑

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The Tumour Node Metastasis (TNM) classification system is recommended for clinical and scientific use [78], but requires continuous re-assessment [79] with the latest version published in 2017. A supplement was published in 2012 (Table 4.1), and the latter's prognostic value was confirmed in single and multi-institution studies [80, 81]. Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system (Table 4.1). However, some uncertainties remain:

- The sub-classification of T1 tumours using a cut-off of 4 cm might not be optimal in NSS for localised cancer.
- The value of size stratification of T2 tumours has been questioned [82].
- Since the 2002 version, tumours with renal sinus fat invasion have been classified as pT3a.
- Renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion but is nevertheless included in the same pT3a stage group [83-85] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [81].
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [86, 87] (LE: 4).

Table 4.1: 2017 TNM classification system [78] and TNM supplement 2012 [88]

T - Primary Tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney		
T1a	Tumour ≤ 4 cm or less		
T1b	Tumour > 4 cm but ≤ 7 cm		
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
T2a	Tumour > 7 cm but ≤ 10 cm		
T2b	Tumours > 10 cm, limited to the kidney		
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia		
T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia		
T3b	Tumour grossly extends into the vena cava below diaphragm		
T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)		
N - Regional Lymph Nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
M - Distant Metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
TNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

A help desk for specific questions about TNM classification is available at <http://www.uicc.org/tnm>.

4.2 Anatomic classification systems

Objective anatomical classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score, the C-index, an Arterial Based Complexity (ABC) Scoring System and Zonal NePhRO scoring system, have been proposed to standardise the description of renal tumours [89-91]. These systems include assessment of tumour size, exophytic/endophytic properties, proximity to the collecting system and renal sinus, and anterior/posterior or lower/upper pole location.

The use of such a system is helpful as it allows objective prediction of potential morbidity of NSS and tumour ablation techniques. These tools provide information for treatment planning, patient counselling, and comparison of partial nephrectomy (PN) and tumour ablation series. However, when selecting the most optimal treatment option, anatomic scores must always be considered together with patient features and surgeon experience.

5. DIAGNOSTIC EVALUATION

5.1 Symptoms

Many renal masses remain asymptomatic until the late disease stages. More than 50% of RCCs are detected incidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases [81, 92] (LE: 3). The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (6-10%) and correlates with aggressive histology and advanced disease [93, 94] (LE: 3).

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [95] (LE: 3).

5.1.1 Physical examination

Physical examination has a limited role in RCC diagnosis. However, the following findings should prompt radiological examinations:

- palpable abdominal mass;
- palpable cervical lymphadenopathy;
- non-reducing varicocele and bilateral lower extremity oedema, which suggests venous involvement.

5.1.2 Laboratory findings

Commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium [96], coagulation study, and urinalysis (LE: 4). For central renal masses abutting or invading the collecting system, urinary cytology and possibly endoscopic assessment should be considered in order to exclude urothelial cancer (LE: 4).

Split renal function should be estimated using renal scintigraphy in the following situations [97, 98] (LE: 2b):

- when renal function is compromised, as indicated by increased serum creatinine or significantly decreased GFR;
- when renal function is clinically important - e.g., in patients with a solitary kidney or multiple or bilateral tumours.

Renal scintigraphy is an additional diagnostic option in patients at risk of future renal impairment due to comorbid disorders.

5.2 Imaging investigations

Most renal tumours are diagnosed by abdominal US or CT performed for other medical reasons [92] (LE: 3). Renal masses are classified as solid or cystic based on imaging findings.

5.2.1 Presence of enhancement

With solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement [99] (LE: 3). Traditionally, US, CT and MRI are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone. Contrast-enhanced US can be helpful in specific cases [100-102] (LE: 3).

5.2.2 Computed tomography or magnetic resonance imaging

Computed tomography or MRI are used to characterise renal masses. Imaging must be performed before and after administration of intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HUs) before and after contrast administration. A change of fifteen, or more, HUs demonstrates enhancement [103] (LE: 3). Computed tomography or MRI allow accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [73, 104-106] (LE: 3). Abdominal CT provides information on [107]:

- function and morphology of the contralateral kidney [108] (LE: 3);
- primary tumour extension;
- venous involvement;
- enlargement of locoregional LNs;
- condition of the adrenal glands and other solid organs (LE: 3).

Abdominal contrast-enhanced CT angiography is useful in selected cases for detailed information on renal vascular supply [109, 110].

If the results of CT are indeterminate, contrast enhanced ultrasound (CEUS) is a valuable alternative to further characterise renal lesions [6] (LE: 1b).

Magnetic resonance imaging may provide additional information on venous involvement if the extent of an inferior vena cava (IVC) tumour thrombus is poorly defined on CT [111-114] (LE: 3).

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [112, 115] (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored for renal mass assessment [116].

In patients with hereditary RCC who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative.

5.2.3 **Other investigations**

Renal arteriography and inferior venacavography have a limited role in the work-up of selected RCC patients (LE: 3). In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered to optimise treatment decision making [97, 98] (LE: 2a).

Positron-emission tomography (PET) is not recommended [6, 117] (LE: 1b).

5.2.4 **Radiographic investigations to evaluate RCC metastases**

Chest CT is accurate for chest staging [86, 87, 118-120] (LE: 3). There is a consensus that most bone metastases are symptomatic at diagnosis; thus, routine bone imaging is not generally indicated [118, 121, 122] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [121, 123, 124] (LE: 3).

5.2.5 **Bosniak classification of renal cystic masses**

This classification system classifies renal cysts into five categories, based on CT imaging appearance, to predict malignancy risk [125, 126] (LE: 3). This system also advocates treatment for each category (Table 5.1).

Table 5.1: Bosniak classification of renal cysts [125]

Bosniak category	Features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions < 3 cm in size, with sharp margins without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intrarenal, non-enhancing, high attenuation renal lesions ≥ 3 cm. Generally well-marginated.	Follow-up, up to five years. Some are malignant.
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or active surveillance – see Chapter 7. Over 50% are malignant.
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant.

5.3 **Renal tumour biopsy**

Percutaneous renal tumour biopsy can reveal histology of radiologically indeterminate renal masses and can be considered in patients who are candidates for AS of small masses, to obtain histology before ablative treatments, and to select the most suitable form of medical and surgical treatment strategy in the setting of metastatic disease [127-132] (LE: 3).

Renal biopsy is not indicated for comorbid and frail patients who can be considered only for conservative management (watchful waiting) regardless of biopsy results. Due to the high diagnostic accuracy of abdominal imaging, renal tumour biopsy is not necessary in patients with a contrast-enhancing renal mass for whom surgery is planned (LE: 4).

Percutaneous sampling can be performed under local anaesthesia with needle core biopsy and/or fine needle

aspiration (FNA). Biopsies can be performed with US or CT guidance, with a similar diagnostic yield [130, 133] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [127-131, 134] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [127-131] (LE: 3).

Core biopsies should be preferred for the characterisation of solid renal masses (LE: 2a). A SR and meta-analysis of the diagnostic performance and complications of renal tumour biopsy (RTB) was recently performed by this Panel. Fifty-seven articles including a total of 5,228 patients were included in the analysis. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [135]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [127, 130, 133] (LE: 2b).

In experienced centres, core biopsies have a high diagnostic yield, specificity, and sensitivity for the diagnosis of malignancy. The above-mentioned meta-analysis showed that sensitivity and specificity of diagnostic core biopsies for the diagnosis of malignancy are 99.1% and 99.7%, respectively [135] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [128-134, 136] (LE: 2a). If a biopsy is non-diagnostic, and radiologic findings are suspicious for malignancy, a further biopsy or surgical exploration should be considered (LE: 4). Repeat biopsies have been reported to be diagnostic in a high proportion of cases (83-100%) [127, 137-139].

Accuracy of RTBs for the diagnosis of tumour histotype is good. The median concordance rate between tumour histotype on RTBs and on the surgical specimen of the following PN or radical nephrectomy (RN) was 90.3% in the pooled analysis [135].

Assessment of tumour grade on core biopsies is challenging. In the pooled analysis the overall accuracy for nuclear grading was poor (62.5%), but significantly improved (87%) using a simplified two-tier system (high grade vs. low grade) [135] (LE: 2a).

The ideal number and location of core biopsies are not defined. However, at least two good quality cores should be obtained, and necrotic areas should be avoided to maximise diagnostic yield [127, 130, 140, 141] (LE: 4). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [142] (LE: 2b). In cT2 or greater renal masses multiple core biopsies taken from at least four separate solid enhancing areas in the tumour were shown to achieve a higher diagnostic yield and a higher accuracy to identify sarcomatoid features without increasing the complication rate [143].

Core biopsies of cystic renal masses have a lower diagnostic yield and accuracy and are not recommended alone, unless areas with a solid pattern are present (Bosniak IV cysts) [127, 130, 135] (LE: 2b). Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions [131, 136, 137, 144, 145] (LE: 3).

Overall, percutaneous biopsies have a low morbidity [135]. Tumour seeding along the needle tract is anecdotal. Spontaneously resolving subcapsular/perinephric haematomas are reported in 4.3% of cases in a pooled analysis, but clinically significant bleeding is unusual (0-1.4%; 0.7% in the pooled analysis) and generally self-limiting [135].

5.4 Summary of evidence and recommendations for the diagnostic assessment of renal cell cancer

Summary of evidence	LE
Contrast enhanced multi-phasic CT has a high sensitivity and specificity for characterisation and detection of RCC, invasion, tumour thrombus and metastatic RCC.	2
MRI has a slightly higher sensitivity and specificity for small renal masses and tumour thrombus as compared to CT.	2
CEUS has a high sensitivity and specificity for characterisation of renal masses.	2
US, Power-Doppler US and PET-CT have a low sensitivity and specificity for detection and characterisation of RCC.	2

Recommendations	grade	
Use multi-phasic contrast-enhanced computed tomography (CT) for general staging and detection of RCC.	strong	↑↑
Use axial abdominal imaging and CT of the chest for staging of RCC.	strong	↑↑
Use non-ionising modalities, mainly contrast enhanced ultrasound (CEUS), for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses.	weak	↑
Do not use bone scan and/or positron-emission tomography (PET)-CT for staging of RCC.	weak	↓
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	strong	↑↑
Perform a percutaneous biopsy in select patients who are considered for active surveillance.	weak	↑
Use a coaxial technique when performing a renal tumour biopsy.	strong	↑↑
Do not perform a renal tumour biopsy of cystic renal masses.	weak	↓

6. PROGNOSTIC FACTORS

6.1 Classification

Prognostic factors can be classified into: anatomical, histological, clinical, and molecular.

6.2 Anatomical factors

Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [78] (Table 4.1).

6.3 Histological factors

Histological factors include tumour grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system [146]. Fuhrman nuclear grade is the most widely accepted grading system [147]. Although affected by intra- and inter-observer discrepancies, Fuhrman nuclear grade is an independent prognostic factor [148]. A simplified two- or three-strata system may be as accurate for prognostication as the classical four-tiered grading scheme [149, 150] (LE: 3). The new WHO/ISUP (International Society of Urological Pathology) grading system [151] that will replace the Fuhrman grading, needs to be validated for prognostic systems and nomograms.

In a univariate analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [152, 153]. However, prognostic information provided by the RCC type is lost when stratified to tumour stage [35, 153] (LE: 3).

Differences in tumour stage, grade and CSS between the RCC types are illustrated in Table 6.1.

Table 6.1: Basic characteristics of three main types of RCC [35, 36, 154]

Type	Percentage of RCC	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman grade 3 or 4 [155]	CSS (HR)
clear-cell RCC	80-90%	28%	28.5%	Referent
papillary RCC	6-15%	17.6%	28.8%	0.64 - 0.85
chromophobe RCC	2-5%	16.9%	32.7%*	0.24 - 0.56

* The Fuhrman grading system is validated for ccRCC, but is unreliable for chRCC.

HR = hazard ratio.

In all RCC types, prognosis worsens with stage and histopathological grade (Tables 6.2 and 6.3). The five-year overall survival (OS) for all types of RCC is 49%, which has improved since 2006 probably due to an increase in incidentally detected RCCs and the introduction of tyrosine kinase inhibitors (TKIs) [156, 157]. Sarcomatoid changes can be found in all RCC types and are equivalent to high grade and very aggressive tumours.

Table 6.2: Cancer-specific survival by stage and histopathological grade in RCCs - HR (95% CI) [36].

T1N0M0	Referent
T2N0M0	2.71 (2.17-3.39)
T3N0M0	5.20 (4.36-6.21)
T4N0M0	16.88 (12.40-22.98)
N+M0	16.33 (12.89-20.73)
M+	33.23 (28.18-39.18)
Grade 1	Referent
Grade 2	1.16 (0.94-1.42)
Grade 3	1.97 (1.60-2.43)
Grade 4	2.82 (2.08-3.31)

CI = confidential interval. HR = hazard ratio.

Long-term survival in RCC patients treated by RN or PN between 1970 and 2003; for unilateral, sporadic ccRCC, pRCC or chRCC in a cohort study [154] (Table 6.3).

Table 6.3: Cancer-specific survival of surgically treated patients by RCC type (estimated survival rate in percentage [95% CI])

Survival time	5 years (%)	10 years (%)	15 years (%)	20 years (%)
clear-cell RCC	71 (69-73)	62 (60-64)	56 (53-58)	52 (49-55)
papillary RCC	91 (88-94)	86 (82-89)	85 (81-89)	83 (78-88)
chromophobe RCC	88 (83-94)	86 (80-92)	84 (77-91)	81 (72-90)

Two subgroups of pRCC with different outcomes have been identified [158]. Type 1 have a favourable prognosis. Type 2 are mostly high-grade tumours with a propensity for metastases (LE: 3). For more details, see Section 3.2 Histological diagnosis. Renal cell cancer with Xp 11.2 translocation has a poor prognosis [159]. Its incidence is low, but it should be systematically addressed in young patients. Renal cell cancer type classification has been confirmed by cytogenetic and genetic analyses [155, 160, 161] (LE: 2b).

6.4 Clinical factors

These include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil/lymphocyte ratio, C-reactive protein (CRP) and albumin [95, 162-166] (LE: 3).

6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [167], PTEN (phosphatase and tensin homolog) (cell cycle), E-cadherin, osteopontin [168] CD44 (cell adhesion) [169, 170], CXCR4 [171], and other cell cycle and proliferative markers [64, 172] are being investigated (LE: 3). None of these markers have clearly improved the predictive accuracy of current prognostic systems, none have been externally validated, and their routine use in clinical practice is at present not recommended. Several retrospective studies and large molecular screening programmes have identified mutated genes in ccRCC with distinct clinical outcomes. The expression of the BAP1 and PBRM1 genes, situated on chromosome 3p in a region that is deleted in more than 90% of ccRCCs, have shown to be independent prognostic factors for tumour recurrence [173-175]. These published reports suggest that patients with BAP1-mutant tumours have worse outcomes compared with patients with PBRM1-mutant tumours [174]. Validated data from surgical series can predict relapse using a sixteen gene signature. This signature is likely to be adopted in clinical trials and may be helpful in the clinical setting in due time [176].

The recognition of the potential relevance of immunotherapy as an approach to RCC management is growing. Prognostic information of cytokines and blockade of immune-inhibitory molecules such as PD-L1 have shown promising therapeutic results. Emerging evidence of chromosomal alterations, through Genome-Wide Association Studies (GWAS), miRNA, SNPs and gene methylations all contribute to improving diagnostic and prognostic information. A number of studies have confirmed prognostic information based on gain of chromosomal regions 7q, 8q and 20q, and chromosomal losses of regions 9p, 9q and 14q, which are associated with poor survival. CpG-methylation-based assays also independently predict survival in ccRCC [177, 178]. An international collaboration is currently investigating GWAS loci for prognostic information.

6.6 Prognostic systems and nomograms

Post-operative prognostic systems and nomograms combining independent prognostic factors have been developed and externally validated [179-185]. These may be more accurate than TNM stage or Fuhrman grade alone for predicting survival (LE: 3). An advantage of nomograms is their ability to measure predictive accuracy (PA), allowing all new predictive parameters to be objectively evaluated. Before being adopted, new prognostic variables or systems should demonstrate that its PA is superior to conventional post-operative prognostic schemes [186]. Recently, new pre-operative nomograms with excellent PA have been designed [187, 188].

Table 6.4 summarises the current most relevant prognostic systems.

6.7 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, tumour nuclear grade, and RCC subtype provide important prognostic information [22].	2

Recommendations	grade	
Use the current Tumour, Node, Metastasis classification system.	strong	↑↑
Use grading systems and classify RCC subtype.	strong	↑↑
Use prognostic systems in the metastatic setting.	strong	↑↑
In localised disease do not routinely use integrated prognostic systems or nomograms for patient selection. Prognostic systems or nomograms can provide a rationale for enrolling patients into clinical trials.	weak	↓
Do not use molecular prognostic markers in routine clinical practice.	weak	↓
In patients receiving targeted treatments, use molecular prognostic markers to predict response.	weak	↑

Table 6.4: Anatomical, histological, and clinical variables in the commonly used prognostic models for localised and metastatic RCC

Prognostic Models	Variables	TNM Stage	ECOG PS	Karnofsky PS	RCC related symptoms	Fuhrman grade	Tumour necrosis	Tumour size	Delay between diagnosis and treatment	LDH	Corrected calcium	Haemoglobin	Neutrophil count	Platelet count	
Localised RCC	UISS	x	x			x									
	SSIGN	x				x		x							
	Post-operative Karakiewicz's nomogram	x			x			x							
Metastatic RCC	MSKCC prognostic system			x					x	x	x	x			
	IMDC				x						x		x	x	
	Heng's model			x					x		x	x	x	x	x

ECOG-PS = Eastern Cooperative Oncology Group - performance status; IMDC = International Metastatic Renal Cancer Database Consortium; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status; SSIGN = Stage Size Grade Necrosis; UISS = University of California Los Angeles integrated staging system.

7. DISEASE MANAGEMENT

7.1 Treatment of localised RCC

7.1.1 Introduction

A SR underpins the findings of sections 7.1.2 to 7.2.4.2. The review included all relevant published literature comparing surgical management of localised RCC (T1-2N0M0) [189, 190]. Randomised or quasi-RCTs were included. However, due to the very limited number of RCTs, non-randomised studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included.

7.1.2 Surgical treatment

7.1.2.1 Nephron-sparing surgery vs. radical nephrectomy

Multiple retrospective series as well as one prospective RCT including patients with organ-confined RCC of limited size, respectively T-stage (pT1), have demonstrated a comparable CSS for PN vs. RN [191-195]. However, trials that directly compared both approaches in terms of their oncological safety are rarely available, therefore, the data presented is based on a comparison of data available from retrospective series that have included patient cohorts of different and, in part, limited size.

In addition, PN vs. RN was demonstrated to better preserve general kidney function, thereby lowering the risk of development of metabolic or cardiovascular disorders.

When compared with a radical surgical approach, for NSS, several retrospective analyses of large databases have suggested a decreased cardiac-specific mortality [196, 197] as well as improved OS as compared to RN. However, in some series this held true only for a younger patient population and/or patients without significant comorbidity at the time of the surgical intervention [198, 199]. An analysis of the Medicare database [200] could not demonstrate an OS benefit for patients > 75 years of age when RN or PN were compared with non-surgical management. Another series that addressed this question and also included Medicare patients suggested an OS benefit in an older RCC patient population (75-80 years) when subjected to surgery rather than non-surgical management. Shuch *et al.* compared patients subjected to PN for RCC with a non-cancer, healthy control group via a retrospective database analysis, showing an OS benefit for the cancer cohort, [201]. These conflicting results indicate that unknown statistical confounders hamper the retrospective analysis of population-based tumour registries.

In contrast, the only prospectively randomised but prematurely closed and heavily underpowered, trial available so far did not demonstrate an inferiority of RN vs. PN in terms of OS. Taken together, the OS advantage suggested for PN vs. RN remains an unresolved issue.

It has been suggested that the more pronounced deterioration of renal function after RN negatively affects patients' OS [98, 202]. Patients with a normal pre-operative renal function and a decreased GFR due to surgical treatment, generally present with a stable renal function longer term [203]. In contrast, adverse OS in patients with a pre-existing GFR reduction does not seem to result from further renal function impairment following surgery, but rather from other medical comorbidities causing pre-surgical CKD. However, in particular in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of development of ESKD which requires haemodialysis.

Only a limited number of studies are available addressing quality of life (QoL) following PN vs. RN irrespective of the surgical approach used (open- vs. minimally invasive). Quality of life was ranked higher following PN as compared to RN, but in general, patients' health status deteriorated following both approaches [191, 192, 194, 204-208].

In terms of the intra- and peri-operative morbidity/complications associated with PN vs. RN, there was no difference in the length of hospital stay [192, 193, 207], the number of red blood cell (RBC) units applied [192, 207, 208], or the mean intra-operative blood loss [192, 207]. Complication rates were inconsistently reported and one intervention was not favoured over another [209]. One study indicated a longer operation time for open PN [209], but this was not confirmed by others [210].

In view of the above and since oncological safety (CSS and FS) of PN has been proven to be similar for RN, PN is the treatment of choice for T1b RCC since it preserves kidney function better and in the long term limits development of metabolic as well as cardiovascular disorders. Whether decreased mortality from any cause can be attributed to PN is still unresolved, but in patients with pre-existing CKD, PN is the preferred surgical treatment option as it avoids further deterioration of kidney function, the latter being associated with a higher risk of development of ESKD and the need for haemodialysis.

Partial nephrectomy is unsuitable in some patients with localised RCC due to:

- insufficient volume of remaining parenchyma to maintain proper organ function;
- renal vein thrombosis;
- unfavourable tumour location e.g. adherence to the renal vessels;
- use of anticoagulants.

In these situations the curative therapy is RN including removal of the tumour-bearing kidney. Complete resection of the primary tumour by open- or laparoscopic surgery offers a reasonable chance of cure.

7.1.2.2 Associated procedures

7.1.2.2.1 Adrenalectomy

One prospective NRS compared the outcomes of RN or PN with, or without, ipsilateral adrenalectomy [211]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at five or ten years was seen, with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 were for benign lesions.

7.1.2.2.2 Lymph node dissection for clinically negative lymph nodes (cN0)

The indication for lymph node dissection (LND) together with PN or RN is still controversial [212]. The clinical assessment of LN status is based on the detection of an enlargement of LNs; either by CT/MRI or the intra-operative palpability of enlarged nodes. Less than 20% of suspected metastatic nodes (cN+) are positive for metastatic disease at histopathological examination (pN+) [213]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [214]. For clinically positive LNs (cN+) see Section 7.2.2.

For patients with clinically negative LNs (cN0) six clinical trials have evaluated the clinical value of LND [212], the latter including one RCT [213] and five comparative studies [215-219].

Smaller retrospective studies have suggested a clinical benefit associated with a more or less extensive lymphadenectomy preferably in patients at high risk for lymphogenic spread. The number of LN metastases (< / > 4) as well as the intra- and extracapsular extension of intranodal metastasis correlated with the patients' clinical prognosis in some studies [214, 220-222]. Better survival outcomes were seen in patients with a low number of positive LNs (< 4) and no extranodal extension. On the basis of a retrospective SEER database analysis of > 9,000 patients no effects of an extended LND on the disease-specific survival (DSS) of patients with pathologically confined negative nodes was demonstrated [223]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of ten for the number of nodes dissected resulted in a 10% absolute increase in DSS. In addition, in a larger cohort of 1,983 patients Capitano *et al.* demonstrated that extended LND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [224].

Only one prospective RCT evaluating the clinical value of LND combined with surgical treatment of primary RCC has been published so far. With an incidence of only 4%, lymphatic spread appears to be very low. Recognising the latter, only a staging effect was attributed to a (super)extended LND [213]. This trial included a very high percentage of patients with pT2 tumours, which are not at increased risk for LN metastases. Additionally, only 25% of patients with pT3 tumours were subjected to a complete LND. The LN template used by the authors was also not clearly stated.

The most optimal surgical approach remains controversial. Retrospective studies suggest that an extended LND should involve the LNs surrounding the ipsilateral great vessel and the inter-aortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of inter-aortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases [214, 215, 225]. At least fifteen LNs should be removed [224, 226]. Sentinel LND is an investigational technique [227, 228].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [229, 230]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [231-233]. These indications will be repeated in Sections 7.2 and 7.3 with cross reference to the summary of evidence and recommendations below.

7.1.2.2.4 Summary of evidence and recommendations

Summary of evidence	LE
The oncological outcome in terms of DSS following PN equals that of a radical approach in patients with c/p T1 RCC.	1b
Ipsilateral adrenalectomy, in the absence of clinical evident adrenal involvement during RN or PN, has no survival advantage.	3
In patients with localised disease without evidence of lymph node metastases, a survival advantage of LND in conjunction with RN is not demonstrated in randomised trials.	1b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	grade	
Offer surgery to achieve cure in localised renal cell cancer.	strong	↑↑
Offer partial nephrectomy to patients with T1 tumours.	strong	↑↑
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	strong	↓↓
Consider an extended lymph node dissection in patients with adverse clinical features including a large diameter of the primary tumour or sarcomatoid histological features.	weak	↑

7.1.3 **Radical and partial nephrectomy techniques**7.1.3.1 *Radical nephrectomy techniques*

No RCTs have assessed oncological outcomes of laparoscopic vs. open RN. A cohort study [234] and retrospective database reviews are available, mostly of low methodological quality [192, 235, 236]. Similar oncological outcomes for laparoscopic vs. open RN were found. Data from one RCT [237] and two NRSs [192, 234] showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic RN group as compared with the open group. Convalescence time was also significantly shorter [234]. No difference in the number of patients receiving blood transfusions was observed, but peri-operative blood loss was significantly less in the laparoscopic arm in all three studies [192, 234, 237]. Surgical complication rates were low with very wide confidence intervals. There was no difference in complications, but operation time was significantly shorter in the open nephrectomy arm. Post-operative QoL scores were similar [192].

Some comparative studies focused on the peri-operative outcomes of laparoscopic vs. RN for renal tumours \geq T2. Overall, patients who underwent laparoscopic RN were shown to have lower estimated blood loss, less post-operative pain, shorter length of hospital stay and convalescence compared to those who underwent open RN [234, 238-240]. Intra-operative and post-operative complications were similar in the two groups [234, 238-241]. No significant differences in CSS, PFS and OS were reported [226, 234, 239, 241, 242] (LE: 2b).

The best approach for RN was the retroperitoneal or transperitoneal approach with similar oncological outcomes in the two RTCs [243, 244] and one quasi-randomised study [245]. Quality of life variables were similar for both approaches.

Hand-assisted vs. standard laparoscopic RN was compared in one RCT [245] and one database review [209]. Estimated five-year OS, CSS, and RFS rates were comparable. Duration of surgery was significantly shorter in the hand-assisted approach, while length of hospital stay and time to non-strenuous activities were shorter for the standard laparoscopic RN cohort [209, 245]. However, the sample size was small.

Robot-assisted laparoscopic RN vs. laparoscopic RN was compared in one study [246]. There were no local recurrences, port-site or distant metastases, but the sample size was small and follow-up was short. Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN [247, 248]. Peri-operative outcomes were similar.

7.1.3.2 *Partial nephrectomy techniques*

Studies comparing laparoscopic PN and open PN found no difference in PFS [249-252] and OS [251, 252] in centres with laparoscopic expertise. The mean estimated blood loss was lower with the laparoscopic approach [249, 251, 253], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events are similar [249, 251]. Operative time is generally longer with the laparoscopic approach [250-252] and warm ischaemia time is shorter with the open approach [249, 251, 253, 254]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [252], but not after follow-up of 3.6 years. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [254]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative

outcomes [255]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [256, 257].

Hand-assisted laparoscopic PN (HALPN) is rarely performed. A recent comparative study of open vs. HALPN showed no difference in OS or RFS at intermediate-term follow-up. The authors observed a lower rate of intra-operative and all-grade post-operative 30-day complications in HALPN than in open PN patients, but there was no significant difference in high Clavien Grade complications. Glomerular filtration rate three months after operation was lower in the HALPN than in the open PN group [258].

The feasibility of off-clamp laparoscopic PN and laparo-endoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm their safety and clinical role [259, 260].

At present, the oncological outcomes of robot-assisted vs. laparoscopic or open PN have been compared only in studies with short-term follow-up. One recent study prospectively compared the peri-operative outcomes of a series of robot-assisted and open PN performed by the same experienced surgeon. Robot-assisted PN was superior to open PN in terms of lower estimated blood loss and shorter hospital stay. Warm ischaemia time, operative time, immediate- early- and short-term complications, variation of creatinine levels, and pathologic margins were similar among the groups [261].

A recent meta-analysis, including a series of NSS, with variable methodological quality compared the peri-operative outcomes of robot-assisted and laparoscopic PN. The robotic group had a significantly lower rate of conversion to open surgery and to radical surgery, shorter warm ischaemia time, smaller change in estimated GFR after surgery and shorter length of stay. No significant difference was observed between the two groups regarding complications, change of serum creatinine after surgery, operative time, estimated blood loss and positive surgical margins (PSMs) [262].

7.1.3.3 Positive margins on histopathological specimens of resected tumours

A positive surgical margin is encountered in about 8% of PNs [263]. Studies comparing different resection techniques (open, laparoscopic, robotic) are inconclusive [264, 265]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite PSMs [266]. A PSM status occurs more frequently in cases in which surgery is imperative, including bilateral tumours [267, 268]. Positive surgical margins increase the risk of disease recurrence, primarily in patients with adverse pathological features (pT2a-pT3a, grade III-IV) [263, 267, 268]. The effect of margin status on long-term oncologic outcomes remains to be determined [264], but PSMs need not translate into worse CSS [267, 268]. Therefore, RN or re-resection of margins presents overtreatment in many cases, but a small percentage of patients will harbour residual malignancy [269]. Patients with PSMs should be informed that they will be subjected to a more intense surveillance (imaging) programme and are at increased risk for secondary local therapies [267, 270]. However, protection from recurrence is not ensured by negative surgical margins [271].

7.1.3.4 Summary of evidence and recommendations

Summary of evidence	LE
Laparoscopic radical nephrectomy has lower morbidity than open surgery.	1b
Oncological outcomes for T1-T2a tumours are equivalent between laparoscopic and open radical nephrectomy.	2a
Partial nephrectomy can be performed, either with an open, pure laparoscopic or robot-assisted approach, based on surgeon's expertise and skills.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared with radical nephrectomy.	3

Recommendations	grade	
Offer laparoscopic radical nephrectomy to patients with T2 tumours and localised masses not treatable by partial nephrectomy.	strong	↑↑
Do not perform radical nephrectomy in patients with T1 tumours for whom partial nephrectomy is indicated.	strong	↓↓

7.1.4 **Therapeutic approaches as alternatives to surgery**

7.1.4.1 *Surgical versus non-surgical treatment*

Population-based studies compared the oncological outcomes of surgery (RN or PN) and non-surgical management for tumours < 4 cm. The analyses showed a significantly lower cancer-specific mortality in patients treated with surgery [200, 272]. However, the patients assigned to the surveillance arm were older and likely to be frailer and less suitable candidates for surgery. Other-cause mortality rates in the non-surgical group significantly exceeded that of the surgical group [272]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [273-275].

7.1.4.2 *Surveillance*

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality [276, 277]. Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (US, CT, or MRI) with delayed intervention reserved for tumours showing clinical progression during follow-up [278]. The concept of AS differs from the concept of watchful waiting. Watchful waiting is reserved for patients whose comorbidities contraindicate any subsequent active treatment and do not require follow-up imaging, unless clinically indicated.

In the largest reported series of AS, the growth of renal tumours was low and progression to metastatic disease was reported in only a limited number of patients [279, 280].

A single-institutional comparative study evaluating patients aged ≥ 75 years showed decreased OS for those who underwent surveillance and nephrectomy relative to NSS for clinically T1 renal tumours. However, patients selected for surveillance were older with greater comorbidity. At multi-variate analysis, management type was not associated with OS after adjusting for age, comorbidity, and other variables [276]. No statistically significant difference in OS and CSS were observed in another study of RN vs. PN vs. AS for T1a renal masses with a follow-up of 34 months [281].

The initial results of the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry were recently published. This prospective, NRS enrolled 497 patients with solid renal masses < 4 cm in size who chose AS or primary active intervention. Patients who selected AS were older, had worse ECOG scores, more comorbidities, smaller tumours, and more often multiple and bilateral lesions. Overall survival for primary intervention and AS was 98% and 96% at two years, and 92% and 75% at five years, respectively ($p = 0.06$). At five years, CSS was 99% and 100%, respectively ($p = 0.3$). Active surveillance was not predictive of OS or CSS in regression modelling with relatively short follow up [282].

Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, AS is appropriate to initially monitor small renal masses, followed, if required, by treatment for progression [278-280, 283-286].

A multicentre study assessed QoL of patients undergoing immediate intervention vs. AS. Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least one year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on AS [287].

7.1.4.3 *Ablative therapies*

7.1.4.3.1 *Cryoablation*

Cryoablation is performed using either a percutaneous or a laparoscopic-assisted approach. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic and percutaneous cryoablation [288-290]. One comparative study reported similar OS, CSS, and RFS in 172 laparoscopic patients with a longer follow up compared with 123 patients treated percutaneously with a shorter follow up [289]. A shorter average length of hospital stay was found with the percutaneous technique [289, 290]. No studies are available comparing surveillance strategies to cryoablation.

A recent SR including 82 articles reported complication rates ranging between 8 and 20% with most complications being minor [291]. Although a precise definition of tumour recurrence is lacking, the authors reported a lower RFS as compared to that of PN.

7.1.4.3.2 *Cryoablation versus partial nephrectomy*

Studies compared open, laparoscopic or robotic PN with percutaneous or laparoscopic cryoablation. Oncological outcomes were mixed, with some studies showing no difference in OS, CSS, RFS, DFS, local recurrence or progression to metastatic disease [292, 293], with some showing significant benefit for the PN techniques for some or all of these outcomes [294-297]. Not all studies reported all outcomes listed, and some were small and included benign tumours. No study showed an oncological benefit for cryoablation over PN.

Peri-operative outcomes, complication rates and other QoL measures were mixed. Some studies found the length of hospital stay was shorter and surgical blood loss was less with cryoablation [292-294], whilst also finding no differences in other peri-operative outcomes such as recovery times, complication rates

or post-operative serum creatinine levels. Two studies [296, 297] reported specific Clavien rates, with mostly non-significant differences, which were mixed for intra-operative vs. post-operative complications. Estimated GFRs were not significantly different in two of the studies, but in favour of cryoablation in a third [295-297]. Estimates of new CKD were also mixed, with one study in favour of cryoablation [295], another strongly in favour of PN [296], and the third showing no difference [297]. One study compared PN with ablation therapy, either cryoablation or RFA [223], and showed significantly improved DSS at both five and ten years for PN.

A recent study compared 1,057 patients treated by PN to 180 treated by RFA and 187 treated by cryoablation for a cT1 tumour and found no difference regarding RFS between the three techniques. Metastasis-free survival was superior after PN and cryoablation compared to RFA for cT1a patients. However, follow-up of patients treated by thermal ablations was shorter [198].

7.1.4.3.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Four studies compared patients with T1a tumours treated by laparoscopic or percutaneous RFA [298-301].

Complications occurred in up to 29% of patients but were mostly minor. Complication rates were similar in patients treated laparoscopically or percutaneously. One study with a limited number of patients [300] found a higher rate of incomplete ablation in patients treated by percutaneous RFA. However, no differences in recurrence or CSS were found in the three comparative studies.

7.1.4.3.4 Radiofrequency ablation versus partial nephrectomy

Most publications about RFA are retrospective cohort studies with a low number of patients and limited follow up. Three studies retrospectively compared RFA to surgery in patients with T1a tumours [302-304].

One study [303] compared T1a patients who underwent either RFA (percutaneous or laparoscopic) or PN and found no difference in OS and CSS. Another study retrospectively reviewed 105 T1a patients treated by percutaneous RFA or RN. Cancer-specific survival was 100% in both groups. Overall survival was lower in the RFA group but patients treated with surgery were younger [302].

In a monocentric study that compared 34 RFA patients to sixteen open PN patients, a higher rate of complications and transfusions was shown in the PN group. Although the tumours were larger in PN patients, progression rates were similar (0%) [304].

A recent meta-analysis [305] reported comparable complication rates and post-operative eGFRs between RFA and PN. The local tumour recurrence rate was higher in the RFA group than in the PN group (OR = 1.81) but there was no difference regarding the occurrence of distant metastasis.

7.1.4.3.5 Cryoablation versus radiofrequency ablation

Two studies compared RFA and cryoablation [306, 307]. No significant differences were reported for OS, CSS, or RFS in either study. For local RFS at five years, one study [306] reported improvement with RFA, while the other [307] reported a benefit with cryoablation. One study [306] reported no differences in Clavien complication rates between the techniques.

7.1.4.3.6 Other ablative techniques

Some studies have shown the feasibility of other ablative techniques, such as microwave ablation, laser ablation, and high-intensity focused US ablation. However, these techniques are considered experimental.

7.1.4.3.7 Summary of evidence and recommendation for therapeutic approaches as alternative to surgery

Summary of evidence	LE
Most population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management.	3
In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).	3
Quality of the available data does not allow definitive conclusions regarding morbidity and oncological outcomes of cryoablation and radiofrequency ablation.	3
Low quality studies suggest a higher local recurrence rate for thermal ablation therapies compared to partial nephrectomy.	3

Recommendation	grade	
Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with small renal masses.	weak	↑

7.2 Treatment of locally advanced RCC

7.2.1 Introduction

In addition to the summary of evidence and recommendations outlined in Section 7.1 for localised RCC, certain therapeutic strategies arise in specific situations for locally advanced disease.

7.2.2 Management of clinically positive lymph nodes (cN+)

In the presence of clinically positive LNs (cN+), LND is always justified [38]. However, the extent of LND remains controversial [214].

7.2.3 Management of locally advanced unresectable RCC

In patients with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [231-233]. The use of neoadjuvant targeted therapy to downsize tumours is experimental and cannot be recommended outside clinical trials.

7.2.4 Management of RCC with venous tumour thrombus

Tumour thrombus formation in the IVC in RCC patients is a significant adverse prognostic factor. Traditionally, patients with venous tumour thrombus undergo surgery to remove the kidney and tumour thrombus. Aggressive surgical resection is widely accepted as the default management option for patients with venous tumour thrombus [308-316]. However, uncertainties remain over the best approach for surgical treatment of these patients.

7.2.4.1 The evidence base for surgery in patients with venous tumour thrombus

The data on whether patients with venous tumour thrombus should undergo surgery is derived from case series. In one of the largest published studies [313] a higher level of thrombus was not associated with increased tumour dissemination to LNs, perinephric fat or distant metastasis. Thus, all patients with non-metastatic disease and venous tumour thrombus, and an acceptable PS, should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation (LE: 3). The surgical technique and approach for each case should be selected based on the extent of tumour thrombus (LE: 3).

7.2.4.2 The evidence base for different surgical strategies

A SR was undertaken which included comparison-only studies on the management of venous tumour thrombus, in non-metastatic RCC [317, 318]. Only five studies were eligible for final inclusion, with high risks of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [319, 320]. Pre-operative embolisation [321] was associated with increased operating time, blood loss, hospital stay and peri-operative mortality in patients with T3 RCC.

No significant differences in oncological and process outcomes were observed between cardiopulmonary bypass with deep hypothermic circulatory arrest or partial bypass under normothermia or single caval clamp without circulatory support [322].

No surgical method was shown to be superior for the excision of venous tumour thrombus. The surgical method was dependent on the level of tumour thrombus, and the grade of occlusion of the IVC [317, 319, 320, 322]. The relative benefits and harms of other strategies and approaches regarding access to the IVC and the role of IVC filters and bypass procedures remain uncertain.

7.2.4.3 Summary of evidence and recommendations for the management of RCC with venous tumour thrombus

Summary of evidence	LE
In patients with locally advanced disease due to clinically enlarged lymph nodes, the survival benefit of lymph node dissection is unclear but lymph node dissection can add staging information.	3
Low quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3
Tumour embolisation or inferior vena cava filter do not appear to offer any benefits.	3

Recommendations	grade	
In patients with clinically enlarged lymph nodes, perform lymph node dissection for staging purposes or local control.	weak	↑
In patients with non-metastatic RCC, excise the kidney tumour and the vena cava thrombus.	strong	↑↑

7.2.5 Adjuvant therapy

There is currently no evidence from randomised phase III trials that adjuvant therapy offers a survival benefit. The impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas remains unconfirmed [323-327] (LE: 1b). Results from prior adjuvant trials studying interferon-alpha (IFN- α) and interleukin-2 (IL-2) did not show a survival benefit [328]. Heat shock protein-peptide complex-96 (vitespen) [329], may have a benefit in a subgroup of patients but the overall data from phase III trials were negative. A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER) [330]. No difference in DFS was observed in the overall trial analysis, but a subgroup evaluation of patients with high CAIX expression suggests a potential benefit of girentuximab in this population. Several RCTs investigating adjuvant sunitinib, sorafenib, pazopanib, axitinib and everolimus are ongoing. At present, there is no evidence for the use of adjuvant VEGF-R or mTOR inhibitors. One of the largest adjuvant trials of sunitinib vs. sorafenib vs. placebo reported in 2015 (ASSURE) after an interim analysis performed with 62% of the data available. Results demonstrated no significant differences in DFS or OS between the experimental arms and placebo and it was concluded that adjuvant therapy with sunitinib or sorafenib should not be given [162]. The S-TRAC study included 615 patients in a 1:1 randomisation (HR: 0.76; 95% CI: 0.59-0.98; $p = 0.03$ for DFS and an immature OS). Grade 3/4 toxicity in the study was 60.5% for patients receiving sunitinib, which translated into significant differences in QoL for loss of appetite and diarrhoea. Based on the conflicting results in the two available studies, the Panel rated the quality of the evidence, harms-benefits ratio, patient preferences and costs. Finally, the panel, including representatives from a patient advocacy group (IKCC), voted and reached a consensus decision to not recommend adjuvant therapy with sunitinib for patients with high-risk RCC after nephrectomy [331].

7.2.5.1 Summary of evidence and recommendations for adjuvant therapy

Summary of evidence	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b
Adjuvant sunitinib improved disease-free survival in one of the two available studies, but not overall survival, after nephrectomy in selected high-risk patients.	1b

Recommendations	grade	
Do not offer adjuvant therapy with sorafenib.	strong	↓↓
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell cancer.	weak	↓

7.3 Advanced/metastatic RCC

7.3.1 Local therapy of advanced/metastatic RCC

7.3.1.1 Cytoreductive nephrectomy

Tumour resection is curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligo-metastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a meta-analysis comparing CN+ immunotherapy vs. immunotherapy only, increased long-term survival was found in patients treated with CN [332]. Only retrospective non-comparative data for CN combined with targeting agents, such as sunitinib, sorafenib and others, are available. Cytoreductive nephrectomy is currently recommended in mRCC patients with a good PS, large primary tumours and low metastatic volume. In patients with poor PS or Metastatic Renal Cancer Database Consortium (IMDC) risk, small primaries and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended.

7.3.1.1.1 Embolisation of the primary tumour

In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [231-233] (see recommendation Section 7.1.2.2.4).

7.3.1.1.2 Summary of evidence and recommendation for local therapy of advanced/metastatic RCC

Summary of evidence	LE
Cytoreductive nephrectomy combined with interferon-alpha improves survival in patients with metastatic RCC and good performance status.	1a
Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3

Recommendation	grade	
Offer cytoreductive nephrectomy to favourable- and intermediate-risk patients with metastatic RCC.	weak	↑

7.3.2 **Local therapy of metastases in mRCC**

A systematic review of the local treatment of metastases from RCC in any organ was undertaken [333]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes assessed were OS, CSS and PFS, local symptom control and adverse events. A risk-of-bias assessment was conducted [334]. Of the 2,235 studies identified only sixteen non-randomised comparative studies were included.

Eight studies reported on local therapies of RCC-metastases in various organs [335-342]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [343-345], two in the brain [346, 347] and one each in the liver [348] lung [349] and pancreas [350]. Three studies [339, 341, 349] were abstracts. Data were too heterogeneous for meta-analysis. There was considerable variation in the type and distribution of systemic therapies (cytokines and VEGF-inhibitors) and in reporting the results.

7.3.2.1 *Complete versus no/incomplete metastasectomy*

All eight studies [335-342] on RCC metastases in various organs compared complete vs. no and/or incomplete metastasectomy. However, in one study [338], complete resections were achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy. Non-surgical modalities were not applied. Six studies [335, 337-339, 341, 342] reported a significantly longer median OS or CSS following complete metastasectomy (the median value for OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one [336] showed no significant difference in CSS between complete and no metastasectomy, and one [340] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases to the lung [349], liver [348], and pancreas [350], respectively. The lung study reported a significantly higher median OS for metastasectomy vs. medical therapy only for both target therapy and immunotherapy. Similarly, the liver and pancreas study reported a significantly higher median OS and five-year OS for metastasectomy vs. no metastasectomy.

7.3.2.2 *Local therapies for RCC bone metastases*

Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases [345]. Single-dose IGRT (≥ 24 Gray) had a significantly better three-year actuarial local PFS rate, also shown by Cox regression analysis. Another study [343] compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations. A significantly higher five-year CSS rate was observed in the intervention group.

After adjusting for prior nephrectomy, gender and age, multi-variate analysis still favoured metastasectomy/curettage and stabilisation. A third study compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy (CRT) in patients with RCC bone metastases to the spine [344]. Pain, objective response rate (ORR), time-to-pain relief and duration of pain relief were similar.

7.3.2.3 *Local therapies for RCC brain metastases*

Two studies on RCC brain metastases were included. A three-armed study [346] compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS + WBRT. Each group was further subdivided into recursive partitioning analysis (RPA) classes I to III (I favourable, II moderate and III poor patient status). Two-year OS and intracerebral control were equivalent in patients treated with SRS alone and SRS + WBRT.

Both treatments were superior to WBRT alone in the general study population and in the RPA subgroup analyses. A comparison of SRS vs. SRS + WBRT in a subgroup analysis of RPA class I showed significantly better two-year OS and intracerebral control for SRS + WBRT based on only three participants. The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy (MTS) + CRT or CRT alone [347]. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. One-, two- and three-year survival rates were higher but not significantly so for FSRT as for metastasectomy + CRT, or CRT alone. Fractionated stereotactic radiotherapy did not result in a significantly better two-year local control rate compared with MTS + CRT.

7.3.2.4 Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [351]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [352] (see recommendation Section 7.1.2.2.4).

7.3.2.5 Summary of evidence and recommendations for local therapy of metastases in metastatic RCC

Summary of evidence	LE
All included studies were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
With the exception of brain and possibly bone metastases, metastasectomy remains by default the only local treatment for most sites.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3

Recommendations	grade	
Consider local therapy for metastatic disease (including metastasectomy) in patients with a favourable risk profile in whom complete resection is achievable or when local symptoms need to be controlled.	weak	↑
Stereotactic radiotherapy for clinically relevant bone or brain metastases can be considered for local control and symptom relief.	weak	↑

7.4 Systemic therapy for advanced/metastatic RCC

7.4.1 Chemotherapy

Chemotherapy is moderately effective only if 5-fluorouracil (5-FU) is combined with immunotherapeutic agents [353]. However, in one study, interferon-alpha (IFN- α) showed equivalent efficacy to IFN- α + interleukin-2 (IL-2) + 5-FU [354].

A combination of gemcitabine and doxorubicin could be an option in sarcomatoid and rapidly progressive RCC [69, 355].

7.4.1.1 Summary of evidence and recommendation for systemic therapy for advanced/metastatic renal cell cancer

Summary of evidence	LE
In metastatic RCC, 5-FU combined with immunotherapy has equivalent efficacy to INF- α .	1b
In metastatic RCC, chemotherapy is otherwise not effective with the exception of gemcitabine and doxorubicine in sarcomatoid and rapidly progressive disease.	3

Recommendations	grade	
Do not offer chemotherapy as first-line therapy in patients with metastatic clear-cell renal cell cancer (RCC).	strong	↓↓
Consider offering a combination of gemcitabine and doxorubicin to patients with sarcomatoid or rapidly progressive RCC.	weak	↑

7.4.2 Immunotherapy

7.4.2.1 IFN- α monotherapy and combined with bevacizumab

Conflicting results exist for IFN- α in clear-cell (cc) mRCC. Several studies showed that IFN- α in mRCC has a survival advantage similar to that of hormonal therapy [356]. Interferon- α resulted in a response rate of 6-15%, a 25% decrease in tumour progression risk and a modest survival benefit compared to placebo [357, 358]. However, patients with intermediate-risk disease, failed to confirm this benefit [359].

Interferon- α may only be effective in some patient subgroups, including patients with ccRCC, favourable-risk criteria, as defined by the Memorial Sloan-Kettering Cancer Center (MSKCC) and lung metastases only [356]. The moderate efficacy of immunotherapy was confirmed in a Cochrane meta-analysis [358]. Bevacizumab + IFN- α increased response rates and PFS in first-line therapy compared with IFN- α monotherapy [360]. All studies comparing targeted drugs to IFN- α monotherapy therapy showed superiority for sunitinib, bevacizumab + IFN- α , and temsirolimus [360-363]. Interferon- α has been superseded by targeted therapy in cc-mRCC.

Table 7.1: The Metastatic Renal Cancer Database Consortium (IMDC) risk model [364]

Risk factors**	Cut-off point used
Karnofsky performance status	< 80%
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)
Absolute neutrophil count (neutrophilia)	> upper limit of normal
Platelets (thrombocytosis)	> upper limit of normal

* The MSKCC (Motzer) criteria are also widely used in this setting [357].

** Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three to six risk factors.

7.4.2.2 Interleukin-2

Interleukin-2 has been used to treat mRCC since 1985, with response rates ranging from 7% to 27% [363, 365, 366]. Complete and durable responses have been achieved with high-dose bolus IL-2, however IL-2 remains the only drug to date that can cure a small percentage of RCC patients. [367]. The toxicity of IL-2 is substantially greater than that of IFN- α [358].

7.4.2.3 Vaccines and targeted immunotherapy

A vaccine trial with tumour antigen 5T4 + first-line standard therapy (i.e. sunitinib, IL-2 or IFN- α) showed no survival benefit compared with placebo and first-line standard therapy [368]. Several vaccination studies are ongoing. Monoclonal antibodies against programmed death-1 (PD-1) or its ligand (PD-1L), which have efficacy and acceptable toxicity in patients with RCC [369], are currently being investigated in phase III trials.

7.4.2.4 Immune checkpoint blockade

Immune checkpoint blockade with monoclonal antibodies target and block the inhibitory T-cell receptor PD-1 or cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) signalling to restore tumour specific T-cell immunity [370]. A randomised dose-ranging phase II trial of nivolumab in metastatic RCC patients revealed a high objective response rate with rapid and durable responses in heavily pre-treated patients [371]. A phase III trial of nivolumab vs. everolimus after one or two lines of VEGF-targeted therapy (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer Grade 3 or 4 adverse events with nivolumab than with everolimus [172, 372, 373]. Nivolumab has superior OS to everolimus ([HR]: 0.73, 95% CI: 0.57-0.93, $p < 0.002$) in VEGF-refractory RCC with a median OS of 25 months for nivolumab and 19.6 months for everolimus (LE: 1b). Patients who had failed multiple lines of VEGF-targeted therapy were included in this trial making the results broadly applicable. The trial included 15% MSKCC poor-risk patients. There was no PFS advantage with nivolumab despite the OS advantage. A phase III trial is currently investigating the combination of nivolumab and ipilimumab vs. sunitinib in first-line treatment (CheckMate 214, NCT 02231749) [167]. Combinations of VEGF-targeted therapy and immune therapy are also being investigated and include:

- Javelin Renal 101 - NCT02684006;
- IMmotion151 - NCT02420821;
- pembrolizumab + axitinib - NCT02133742;
- lenvatinib + everolimus or pembrolizumab - NCT02811861.

7.4.2.5 Summary of evidence and recommendations for immunotherapy in mRCC

Summary of evidence	LE
Interferon- α monotherapy is inferior to VEG-targeted therapy or mTOR inhibition in mRCC.	1b
Interleukin-2 monotherapy may have an effect in selected cases (good PS, ccRCC, lung metastases only).	2
IL-2 has more side-effects than IFN- α .	2
High dose (HD)-IL-2 is associated with durable complete responses in a limited number of patients. However, no clinical factors or biomarkers exist to accurately predict a durable response in patients treated with HD-IL-2.	1b
Bevacizumab plus IFN- α is more effective than IFN- α treatment-naïve, low-risk and intermediate-risk ccRCC.	1b
Vaccination therapy with tumour antigen 5T4 showed no survival benefit over first-line standard therapy.	1b
Cytokine combinations, with or without additional chemotherapy, do not improve OS compared with monotherapy.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b

Recommendations	grade	
Offer nivolumab after one or two lines of vascular endothelial growth factor-targeted therapy in metastatic RCC.	strong	↑↑
Do not offer monotherapy with interferon- α or high-dose bolus interleukin-2 as first-line therapy in metastatic RCC.	weak	↓

7.4.3 Targeted therapies

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL-inactivation results in over-expression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [374-376]. This process substantially contributes to the development and progression of RCC. There are several targeting drugs approved for treating mRCC in both the USA and Europe.

Most published trials have selected for clear-cell carcinoma subtypes, thus no robust evidence-based recommendations can be given for non-ccRCC subtypes.

In major trials leading to registration of the approved targeted agents, patients were stratified according to the MSKCC risk model [356] (Table 7.1). Since the MSKCC (Motzer) criteria were developed during the cytokine era, the IMDC risk model has been established and validated to aid accurate prognosis of patients treated in the era of targeted therapy. Neutrophilia and thrombocytosis have been added to the list of MSKCC risk factors, while LDH has been removed [364].

The IMDC published data on conditional survival which may be used in patient counselling [377]. The IMDC risk model has been validated and compared with the Cleveland Clinic Foundation (CCF) model, the French model, MSKCC model, and the International Kidney Cancer Working Group (IKCWG) model. The IMDC model did not differ from the other models, indicating that a ceiling has been reached in predicting prognosis based solely on clinical factors [378]. Both the MSKCC and IMDC developed models for second-line treatment in the era of targeted therapy based, in part, on their risk models for treatment-naïve patients [379].

Table 7.2: Median OS and percentage of patients surviving two years treated in the era of targeted therapy per IMDC risk group (based on references [364, 378])

IMDC Model	Patients**		Median OS* (months)	2-y OS (95% CI)**
	n	%		
Favourable	157	18	43.2	75% (65-82%)
Intermediate	440	52	22.5	53% (46-59%)
Poor	252	30	7.8	7% (2-16%)

* Based on [378]; ** based on [364]

CI = confidence interval; IMDC = Metastatic Renal Cancer Database Consortium; OS = overall survival.

7.4.3.1 Tyrosine kinase inhibitors

7.4.3.1.1 Sorafenib

Sorafenib is an oral multi-kinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS [380] (HR: 0.44; 95% CI: 0.35-0.55; $p < 0.01$). Overall survival improved in patients initially assigned to placebo who were censored at crossover [381]. In patients with previously untreated mRCC sorafenib was not superior to IFN- α (phase II study). A number of studies have used sorafenib as the control arm in sunitinib-refractory disease vs. axitinib, dovitinib and temsirolimus. None showed superior survival for the study drug compared to sorafenib.

7.4.3.1.2 Sunitinib

Sunitinib is an oral tyrosine kinase (TK) inhibitor and has anti-tumour and anti-angiogenic activity. Sunitinib as second-line monotherapy (after cytokines) in patients with mRCC demonstrated a partial response in 34-40% and stable disease at > 3 months in 27-29% of patients [382]. First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN- α . Overall survival was greater in patients treated with sunitinib (26.4) vs. INF- α (21.8 months) despite crossover [383].

In the EFFECT trial, sunitinib 50 mg/day (four weeks on/two weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with cc-mRCC [384]. Median time to progression (TTP) with sunitinib 50 mg was numerically longer than the 37.5 mg arm (9.9 months vs. 7.1 months). No significant differences in OS were seen (23.1 vs. 23.5 months; $p = 0.615$). Toxicity was comparable in both arms. Because of the non-significant, but numerically longer TTP with the standard 50 mg dosage, the authors recommended using this regimen. Alternate scheduling of sunitinib (two weeks on/one week off) is being used to manage toxicity, but robust data to support its use is lacking [385].

7.4.3.1.3 Pazopanib

Pazopanib is an oral angiogenesis inhibitor. In a trial of pazopanib vs. placebo in treatment-naïve mRCC patients and cytokine-treated patients, a significant improvement in PFS and tumour response was observed [386]. Median PFS with pazopanib compared with placebo was:

- 9.2 vs. 4.2 months in the overall study population;
- 11.1 vs. 2.8 months for the treatment-naïve subpopulation;
- 7.4 vs. 4.2 months for the cytokine-pre-treated subpopulation.

A trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as another first-line option. It showed that pazopanib was not associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles [387], and QoL was better with pazopanib. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%; $p < 0.05$) due to symptomatic toxicity [388]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

7.4.3.1.4 Axitinib

Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3. Axitinib was first evaluated as second-line treatment. In the AXIS trial, axitinib was compared to sorafenib in patients with previously failed cytokine treatment or targeted agents (mainly sunitinib) [389].

The overall median PFS was greater for axitinib than sorafenib. The difference in PFS was greatest in patients in whom cytokine treatment had failed. For those in whom sunitinib had failed, axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months). Axitinib showed $>$ Grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11%. Across all grades, nausea was recorded in 32%, vomiting in 24%, and asthenia in 21%. Overall survival was a secondary end-point of the trial in which crossover was not permitted. Final analysis of OS showed no significant differences between axitinib or sorafenib [390, 391].

In a randomised phase III trial of axitinib vs. sorafenib in first-line treatment-naïve cc-mRCC, a significant difference in median PFS between the treatment groups was not demonstrated [392]. As a result of this study, axitinib is not approved for first-line therapy.

7.4.3.1.5 Cabozantinib

Cabozantinib is an oral inhibitor of TK, including MET, VEGF and AXL. Cabozantinib was investigated in a phase I study in patients resistant to VEGFR and mTOR inhibitors demonstrating objective responses and disease control [171]. Based on these results a randomised phase III trial investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [64]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease by 42% (HR: 0.58 95% CI: 0.45-0.75) [64] (LE: 1b). The median PFS for cabozantinib was 7.4 months (95% CI: 5.6-9.1) vs. 3.8 months (95% CI: 3.7-5.4) for everolimus. The trial recruited 658 patients although PFS was assessed on the first 375 patients. The median OS was 21.4 months (95% CI: 18.7 to not estimable) with cabozantinib and 16.5 months (95% CI 14.7-18.8) with everolimus in VEGF-resistant RCC. The HR for death was 0.66 (95% CI: 0.53-0.83; $p = 0.0003$) [393]. Grade 3 or 4 adverse events were reported in 74% with cabozantinib and 65% with everolimus. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib. Discontinuation due to toxicity was not significantly different for the two drugs. The trial included 16% MSKCC poor-risk patients.

7.4.3.1.6 Lenvatinib

Lenvatinib is an oral multi-target TKI of VEGFR1, VEGFR2, and VEGFR3, with inhibitory activity against fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3, and FGFR4), platelet growth factor receptor α (PDGFR α), re-arranged during transfection (RET), and receptor for stem cell factor (KIT). It has recently been investigated in randomised phase II study in combination with everolimus vs. lenvatinib or everolimus alone (see Section 7.4.6.1.1.5 for discussion of results).

7.4.4 **Monoclonal antibody against circulating VEGF**

7.4.4.1 *Bevacizumab monotherapy and bevacizumab + IFN- α*

Bevacizumab is a humanised monoclonal antibody. The double-blind AVOREN study compared bevacizumab + IFN- α with IFN- α monotherapy in mRCC [360]. Overall response was higher in the bevacizumab + IFN- α group. Median PFS increased from 5.4 months with IFN- α to 10.2 months with bevacizumab + IFN- α . No benefit was seen in MSKCC poor-risk patients. Median OS in this trial, which allowed crossover after progression, was not greater in the bevacizumab/IFN- α group (23.3 vs. 21.3) [394].

An open-label trial (CALGB 90206) [395, 396], of bevacizumab + IFN- α vs. IFN- α showed a higher median PFS for the combination group. Objective response rate was also higher in the combination group. Overall toxicity was greater for bevacizumab + IFN- α , with significantly more Grade 3 hypertension, anorexia, fatigue, and proteinuria.

7.4.5 **mTOR inhibitors**

7.4.5.1 *Temsirolimus*

Temsirolimus is a specific inhibitor of mTOR [397]. Patients with modified high-risk mRCC in the NCT00065468 trial received first-line temsirolimus or IFN- α monotherapy, or a combination of both [362]. Median OS was higher in the temsirolimus group. However, OS in the temsirolimus + IFN- α group was not significantly superior to IFN- α alone [362]. Interferon- α toxicity was marked, partly due to the high doses used. The INTORSECT trial investigated temsirolimus vs. sorafenib in patients who had previously failed sunitinib. Although no benefit in PFS was observed, a significant OS benefit for sorafenib was noted [398]. Based on these results, temsirolimus is not recommended in patients with VEGF TKI-refractory disease.

7.4.5.2 *Everolimus*

Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus + best supportive care (BSC) vs. placebo + BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF-targeted therapy) [399]. The initial data showed a median PFS of four months vs. 1.9 months for everolimus and placebo, respectively [399]. This was extended to 4.9 months in the final analysis (HR: 0.33) [400]. Subset analysis of PFS for patients receiving only one previous VEGF TKI was 5.4 months [401]. This included some patients who were intolerant rather than progressed on therapy (PFS was also 5.4 months) [402]. RECORD-1 included patients who failed multiple lines of VEGF-targeted therapy, and received everolimus in a third- and fourth-line setting [399].

The RECORD-3 randomised phase II study of sequential first-line sunitinib and second-line everolimus vs. sequential first-line everolimus and second-line sunitinib in treatment-naïve mRCC reported a higher median

PFS for first-line treatment in the sunitinib group [403]. Primary endpoint was to assess PFS non-inferiority of first-line everolimus to first-line sunitinib. A large number of the crossover patients did not receive the planned subsequent therapy making further analysis complex and underpowered.

7.4.6 **Therapeutic strategies**

7.4.6.1 *Therapy for treatment-naïve patients with clear-cell mRCC*

Key trials have established sunitinib, pazopanib and bevacizumab plus IFN- α as first-line treatment options in treatment-naïve patients with cc-mRCC and a favourable-to-intermediate risk score. The evidence for subsequent therapies after temsirolimus in poor-risk patients is unclear. It is therefore more appealing to treat poor-risk patients with sunitinib or pazopanib, both of which were tested in pivotal trials in this population.

7.4.6.1.1 Sequencing targeted therapy

7.4.6.1.1.1 Following progression of disease with one or more lines of VEGF-targeted therapy

Several trials investigated therapeutic options for patients who progressed on first-line VEGF-targeted therapy, including studies which investigated options after one or more lines of VEGF-targeted therapy. RECORD-1 established VEGF TKI therapy until disease progression, followed by everolimus as one of the treatment options for patients with mRCC [399]. However, both nivolumab and cabozantinib were superior to everolimus following a similar trial design as RECORD-1 [172]. Both of these agents should be considered a new standard of care in patients of all risk categories who have failed one or more VEGF-targeted therapies (Figure 7.1).

Nivolumab should be considered for all patients in whom it is not contraindicated in the VEGF-refractory setting owing to a significant OS advantage compared to everolimus, as well as its attractive tolerability profile. Cabozantinib is the first TKI to have both a superior PFS and OS compared to everolimus. Both nivolumab and cabozantinib have different toxicity profiles.

Axitinib is superior to sorafenib in terms of PFS in sunitinib-refractory ccRCC [388]. Neither nivolumab nor cabozantinib has been tested directly against axitinib in the second-line setting. However, the OS advantage of both drugs and tolerability of nivolumab over everolimus in this setting makes them preferable to axitinib.

Tolerability is an important consideration when recommendations cannot be made for efficacy alone. Both everolimus and sorafenib have been outperformed by other agents in VEGF-refractory disease and should not be the standard of care in pure VEGF-refractory disease where superior alternatives are available. It is not currently possible to determine therapy based on baseline characteristics or biomarker expression for any of the above drugs.

Direct comparison of RECORD-1, Checkmate-25 and METEOR data with AXIS data is not advised due to differences in patient populations [389-391, 399].

INTORSECT compared temsirolimus vs. sorafenib after disease progression on sunitinib [398]. Median PFS was higher, but not significant, in the temsirolimus group. However, there was a significant difference in OS in favour of sorafenib. Neither of these agents are recommended or widely used in this setting. These data are not necessarily relevant to other mTOR inhibitors such as everolimus.

Based on difference in OS, recommendations can currently be made as to the best sequence of targeted therapy (Figure 7.1). Two major trials, testing nivolumab and cabozantinib, have changed treatment paradigms in VEGF-refractory RCC (LE: 1a). There is a strong rationale for using both drugs in sequence in the second and third line following VEGF-targeted therapy. This creates a new a standard for the majority of patients.

7.4.6.1.1.2 Treatment after progression of disease with mTOR inhibition

There are limited data addressing this issue. In view of the efficacy of VEGF-targeted therapy in renal cancer, a switch to VEGF-targeted therapy is advised (Panel consensus in conjunction with Motzer *et al.* [404]).

7.4.6.1.1.3 Treatment after progression of disease with cytokines

Trials have established sorafenib, axitinib and pazopanib as therapeutic options in this setting with a median PFS of 5.5, 12.1 and 7.4 months, respectively. Based on trial data, axitinib is superior to sorafenib in patients previously treated with cytokine therapy [389-391].

7.4.6.1.1.4 Treatment after second-line targeted therapy

7.4.6.1.1.4.1 Treatment after two VEGF-targeted therapies

Based on the results of the nivolumab and cabozantinib trials, a strong rationale exists for preferring both drugs as third-line treatment upon failure of two VEGF-targeted therapies [64, 172] (Figure 7.1).

7.4.6.1.1.4.2 Treatment after VEGFR- and mTOR inhibition

Although the GOLD trial failed to demonstrate superior efficacy of dovitinib over sorafenib in patients with mRCC who experienced disease progression after receiving prior VEGF- and mTOR-targeted therapies, the results suggest efficacy and safety of sorafenib in the third-line setting [404]. This sequence is not recommended when alternative superior drugs are available.

7.4.6.1.1.4.3 Combination of targeted agents

No combinations of targeted agents are currently recommended, however, there have been a number of trials with VEGF-targeted therapy and mTOR inhibitors [405-409]. A small randomised phase II trial in which 153 patients received either lenvatinib plus everolimus (n = 51), single-agent lenvatinib (n = 52), or single-agent everolimus (n = 50) demonstrated a PFS benefit for the combination [410]. Lenvatinib plus everolimus significantly prolonged PFS compared with everolimus alone (median 14.6 months [95% CI: 5.9-20.1] vs. 5.5 months [3.5-7.1]; HR: 0.40; 95% CI: 0.24-0.68; p = 0.0005), but not compared with lenvatinib alone (7.4 months [95% CI: 5.6-10.2]; HR: 0.66; 95% CI: 0.30-1.10; p = 0.12). In a post-hoc updated analysis (data cut-off Dec 10, 2014), the difference in OS between lenvatinib plus everolimus vs. single-agent everolimus was significantly increased, median OS 25.5 months [95% CI: 16.4-NE] vs. 15.4 months [11.8-19.6]; HR: 0.51; 95% CI: 0.30-0.88; p = 0.024. Grade 3 or worse serious adverse events occurred in 23 (45%) patients allocated to lenvatinib plus everolimus, 23 (44%) allocated to single-agent lenvatinib, and 19 (38%) allocated to single-agent everolimus.

7.4.6.2 *Non-clear-cell renal cancer*

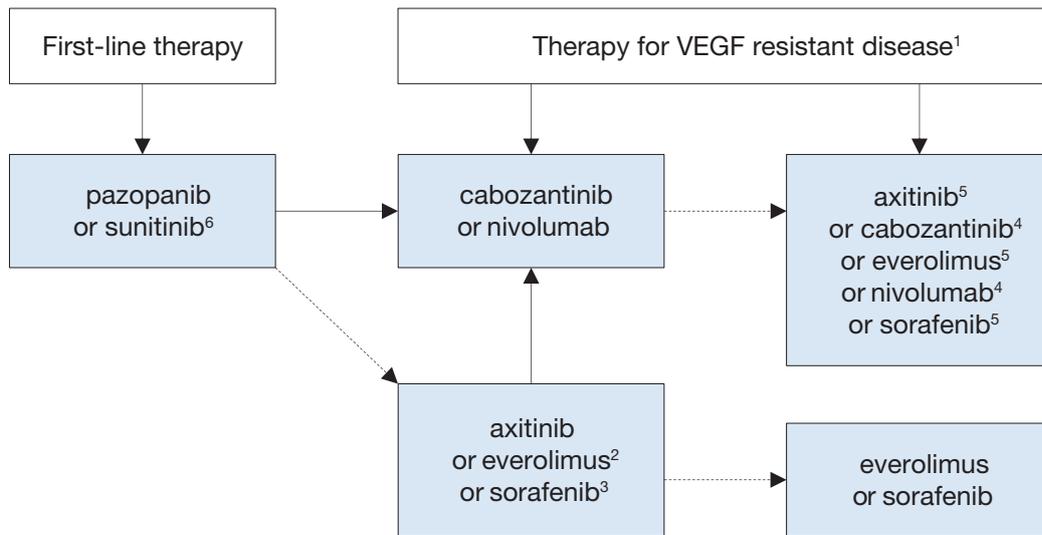
No phase III trials of patients with non-ccRCC have been reported. Expanded access programmes and subset analysis from RCC studies suggest the outcome of these patients with targeted therapy is poorer than for ccRCC. Targeted treatment in non-ccRCC has focused on temsirolimus, everolimus, sorafenib and sunitinib [362, 411-413].

The most common non-clear-cell subtypes are papillary type 1 and non-type 1 papillary RCCs. There are small single-arm trials for sunitinib and everolimus [413-416]. A trial of both types of pRCC treated with everolimus (RAPTOR) [416], showed a median PFS of 3.7 months per central review in the intention-to-treat population with a median OS of 21.0 months.

Another trial investigated foretinib (a dual MET/VEGFR2 inhibitor) in patients with pRCC. Toxicity was acceptable with a high relative risk in patients with germline MET mutations [417]. However, a randomised phase II trial of everolimus vs. sunitinib (ESPN) with crossover design in non-cc-mRCC including 73 patients (27 with pRCC) was stopped after a futility analysis for PFS and OS [418]. The final results presented at the 2014 annual meeting of the American Society of Clinical Oncology showed a non-significant trend favouring sunitinib (6.1 vs. 4.1 months). Based on a SR including subgroup analysis of the ESPN, RECORD-3 and another phase II trial (ASPEN) sunitinib and everolimus remain options in this population, with a preference for sunitinib [136, 419, 420]. Patients with non-cc-mRCC should be referred to a clinical trial where appropriate.

Collecting-duct cancers are resistant to systemic therapy. There is a lack of data to support specific therapy in these patients. There is limited data supporting the use of targeted therapy in other histological subtypes such as chromophobe tumours [362, 411].

Figure 7.1: Recommendations for patients with metastatic ccRCC who have failed one or more lines of VEGF targeted therapy



¹ Switch to therapies not given previously.
² Nivolumab and cabozantinib have not been given after everolimus and therefore cannot be recommended above other agents.
³ Sorafenib has an inferior progression-free survival to axitinib.
⁴ These drugs have shown a survival advantage in VEGF-resistant disease but not in this specific setting.
⁵ These drugs were given after progression in the pivotal cabozantinib or nivolumab trials [64, 172].
⁶ Sunitinib and pazopanib can be recommended in all MSKCC risk groups. Bevacizumab/interferon (favourable- and intermediate-risk disease) and temsirolimus (poor-risk disease) have not been widely used as first-line therapy in the pivotal VEGF-resistant trials and therefore recommendations are not possible.

Table 7.3: EAU 2017 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [356]	First-line	LE [^]	Second-Line after VEGF therapy*	LE [^]	Third-line*	LE [^]	Later lines	LE
Clear cell*	Favourable, intermediate and poor	sunitinib pazopanib bevacizumab + IFN- α (favourable-intermediate only)	1b 1b 1b	based on OS: nivolumab cabozantinib based on PFS: axitinib sorafenib [#] everolimus ^{&}	2b 2b 2b 2b 2b	after VEGF therapy: nivolumab cabozantinib everolimus ^{&} after VEGF and mTOR therapy: sorafenib after VEGF and nivolumab: cabozantinib axitinib everolimus	2b 2b 2b 1b 4 4 4	any targeted agent	4
Clear cell*	poor	temsirolimus sunitinib pazopanib	1b 2b 2b	any targeted agent	4				

Non-clear cell §	any	sunitinib	1b^^	Any targeted agent	4				
<p><i>IFN-α = interferon alpha; LE = level of evidence; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; RCC = renal cell cancer; TKI= tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.</i></p> <p>*Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg bi-weekly intravenously; sunitinib 50 mg daily orally for four weeks, followed by two weeks of rest (37.5 mg continuous dosing did not show significant differences); temsirolimus 25 mg weekly intravenously; pazopanib 800 mg daily orally. Axitinib 5 mg twice daily, to be increased to 7 mg twice daily, unless greater than Grade 2 toxicity, blood pressure higher than 150/90 mmHg, or the patient is receiving antihypertensive medication. Everolimus, 10 mg daily orally.</p> <p>§ No standard treatment available. Patients should be treated in the framework of clinical trials or a decision can be made in consultation with the patient to perform treatment in line with ccRCC.</p> <p>¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC [356] risk plus metastases in multiple organs. Evidence for subsequent therapies unclear, making this option less appealing.</p> <p># Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS [391].</p> <p>^ Level of evidence was downgraded in instances when data were obtained from subgroup analysis within a RCT.</p> <p>& Everolimus was inferior in terms of OS to nivolumab and in terms of PFS to cabozantinib and should not routinely be given where other superior agents are available.</p> <p>^^ Based on a SR [420].</p>									

7.4.6.3 Summary of evidence and recommendations for systemic therapy in metastatic renal cell cancer

Summary of evidence	LE
VEGF and TKIs increase PFS and/or OS as both first-line and second-line treatments for clear-cell mRCC.	1b
Axitinib has proven efficacy and superiority in PFS as a second-line treatment after failure of cytokines and VEGF-targeted therapy in comparison with sorafenib.	1b
Sunitinib is more effective than IFN-α in treatment-naïve patients.	1b
Bevacizumab plus IFN-α is more effective than IFN-α in treatment-naïve low-risk and intermediate-risk patients.	1b
pazopanib is superior to placebo in both naïve mRCC patients and post-cytokine patients.	1b
First line pazopanib is not inferior to sunitinib in clear-cell mRCC patients.	1b
Temsirolimus monotherapy prolongs OS compared to IFN-α in poor-risk mRCC.	1b
Nivolumab is superior to everolimus in terms of OS and adverse events in patients failing one or two lines of VEGF-targeted therapy.	1b
Cabozantinib is superior to everolimus in terms of PFS and OS in patients failing one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS in patients who have previously failed or are intolerant of VEGF-targeted therapy when compared to placebo.	1b
Sorafenib has broad activity in a spectrum of settings in ccRCC patients previously treated with cytokine or targeted therapies. It is inferior to axitinib in both sunitinib or cytokine pre-treated patients.	4
Both mTOR inhibitors (everolimus and temsirolimus) and VEGF-targeted therapies (sunitinib or sorafenib) can be used in non-clear cell RCC.	3
No combination has proven to be better than single-agent therapy, with the exception of the combination of lenvatinib plus everolimus.	1a

Recommendations	grade	
Offer sunitinib or pazopanib as first-line therapy for metastatic clear-cell renal cell cancer (ccRCC).	strong	↑↑
Consider offering bevacizumab + Interferon (IFN)- α as first-line therapy for metastatic RCC in favourable and intermediate-risk ccRCC.	weak	↑
Consider offering temsirolimus as first-line treatment in poor-risk RCC patients.	weak	↑
Offer cabozantinib for ccRCC after one or two lines of vascular endothelial growth factor (VEGF)-targeted therapy in metastatic RCC.	strong	↑↑
Offer nivolumab after one or two lines of VEGF-targeted therapy in metastatic RCC.	strong	↑↑
Offer axitinib or everolimus to ccRCC patients who failed VEGF-targeted therapy, and when nivolumab or cabozantinib are not safe, tolerable or available.	strong	↑↑
Sequence targeted agents in treating metastatic RCC.	strong	↑↑
Sunitinib can be offered as first-line therapy for non-clear cell mRCC.	weak	↑

7.5 Recurrent RCC

7.5.1 Introduction

Locally recurrent disease can occur after RN, PN and thermal ablation. After nephron-sparing treatment the recurrence may be intrarenal and/or regional, e.g. venous tumour thrombi or retroperitoneal LN metastases. Both are often summarised as loco-regional recurrences. Recurrence for pT1 tumours after PN are observed in 2.2% and are generally managed surgically depending on the extent of the loco-regional recurrence [421]. After thermal ablation loco-regional recurrences (intrarenal and regional) have been described in up to 12% [422]. Repeated ablation has often been recommended for intrarenal recurrences following thermal ablation. For loco-regional recurrences surgical resection is mandatory and has been described for isolated local recurrences following nephrectomy.

After nephrectomy locally recurrent disease is defined as disease recurring in the renal fossa or remnant kidney. However, metastasis in the non-removed ipsilateral adrenal or non-resected LNs makes interpretation of the true incidence of isolated recurrence in the renal fossa difficult. Treatment of adrenal metastases or LN metastases are often described in series of metastasectomy (see Section 7.3). Isolated local recurrence, however, is rare.

The largest series on the treatment of isolated recurrence was published in 2009 [423]. In 2,945 patients who underwent nephrectomy the authors identified 54 isolated local recurrences in the renal fossa. These, however, included recurrences to the ipsilateral adrenal and LNs. Exclusively retrospective non-comparative data exist which suggest that aggressive local resection offers durable local tumour control and improves survival. Adverse prognostic factors were, a positive surgical margin after resection, the size of the recurrence and sarcomatoid histologic features [423]. In cases where complete surgical removal is not feasible due to advanced tumour growth and pain, palliative treatments including radiation treatment can be considered.

7.5.2 Summary of evidence and recommendation for advanced/metastatic RCC

Summary of evidence	LE
Isolated recurrence in the local renal fossa is rare.	3
Patients who undergo resection of local recurrences in the absence of sarcomatoid features may benefit from durable local control and improved survival.	3

Recommendation	grade	
Offer surgical resection of local recurrent disease, when feasible.	weak	↑

8. FOLLOW-UP IN RCC

8.1 Introduction

Surveillance after treatment for RCC allows the urologist to monitor or identify:

- post-operative complications;
- renal function;
- local recurrence;
- recurrence in the contralateral kidney;
- development of metastases.

There is no consensus on surveillance after RCC treatment, and there is no evidence that early vs. later diagnosis of recurrences improves survival. However, follow-up is important to increase the available information on RCC, and should be performed by a urologist, who should record the time to recurrence or the development of metastases. Patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [424].

An individualised, risk-based, approach to RCC surveillance was recently proposed. The authors use competing risk models, incorporating patient age, pathologic stage, relapse location and comorbidities, to calculate when the risk of non-RCC death exceeds the risk of RCC recurrence [425]. For patients with low-stage disease but with a Charlson comorbidity index ≥ 2 , the risk of non-RCC death exceeded that of abdominal recurrence risk already one month after surgery, regardless of patient age.

Renal function is assessed by the measurement of serum creatinine and eGFR. Repeated long-term monitoring of eGFR is indicated in case of impaired renal function before, or after, surgery. Renal function [426, 427] and non-cancer survival [196, 428, 429] can be optimised by performing NSS, whenever possible, for T1 and T2 tumours [430] (LE: 3). Recurrence after PN is rare, but early diagnosis is useful, as the most effective treatment is redux surgery [431, 432]. Recurrence in the contralateral kidney is also rare and might be related to positive margins, multifocality, and grade [433] (LE: 3). Surveillance can identify local recurrences or metastases at an early stage. In metastatic disease, extended tumour growth can limit the opportunity for surgical resection, which is considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, early diagnosis of tumour recurrence may enhance the efficacy of systemic treatment if the tumour burden is low.

8.2 Which investigations for which patients, and when?

There is no high level evidence to support any surveillance scheme. However, intensive radiological surveillance for all patients is not necessary. The outcome after surgery for T1a low-grade tumours is almost always excellent. It is therefore reasonable to stratify the follow up, taking into account the risk of developing recurrence or metastases. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up periods [35, 434, 435] (LE: 4). One study has shown a survival benefit for patients who were followed within a structured surveillance protocol vs. patients who were not [424]:

- The sensitivity of chest radiography and US for small metastases is poor. Surveillance with these imaging modalities should not be done [436].
- In low-risk tumours, surveillance intervals should be adapted taking into account radiation exposure and benefit. To reduce radiation exposure, MRI can be used outside the thorax.
- When the risk of relapse is intermediate or high, CT of the chest and abdomen should be performed.
- Surveillance should also include evaluation of renal function and cardiovascular risk factors.
- Positron-emission tomography and PET-CT as well as bone scintigraphy should not be used in RCC surveillance, due to their limited specificity and sensitivity.
- The risk of acute renal failure seems to be negligible in patients with a GFR > 20 mL/min and chronic renal impairment [437].

Controversy exists on the optimal duration of follow-up. Some argue that follow-up with imaging is not cost-effective after five years; however, late metastases are more likely to be solitary and justify more aggressive therapy with curative intent. In addition, patients with tumours that develop in the contralateral kidney can be treated with NSS if the tumours are detected early. For tumours < 4 cm, there is no difference between PN and RN with regard to recurrences during follow up [438] (LE: 3).

Several authors [182, 184, 439, 440], have designed scoring systems and nomograms to quantify the likelihood of patients developing tumour recurrences, metastases, and subsequent death. These systems have been compared and validated [441] (LE: 2). Using prognostic variables, several stage-based surveillance

regimens have been proposed [442, 443], but none include ablative therapies. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [179]. Recently, a pre-operative prognostic model based on age, symptoms, and TNM staging has been published and validated [188] (LE: 3). A surveillance algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient's risk profile, but also efficacy of the treatment given (Table 8.1). These prognostic systems can be used to adapt the surveillance schedule according to suspected risk of recurrence.

Data from adjuvant trials are generally based on the University of California Los Angeles integrated staging system (UISS) risk stratification, which makes it the most widely used, and validated system [162, 444].

Table 8.1: Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy

Risk profile	Surveillance						
	6 mo	1 y	2 y	3 y	4 y	5 y	> 5 y
Low	US	CT	US	CT	US	CT	Discharge
Intermediate	CT	CT	CT	US	CT	CT	CT once every 2 years
High	CT	CT	CT	CT	CT	CT	CT once every 2 years

CT = computed tomography of chest and abdomen, alternatively use MRI;

US = ultrasound of abdomen, kidneys and renal bed.

8.3 Summary of evidence and recommendations for surveillance following RN or PN or ablative therapies in RCC

Summary of evidence	LE
Surveillance can detect local recurrence or metastatic disease while the patient is still surgically curable.	4
After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a positive surgical margin.	3
Patients undergoing surveillance have a better overall survival than patients not undergoing surveillance.	3

Recommendations	grade	
Base follow-up after RCC on the risk of recurrence.	strong	↑↑
For low-risk disease, computed tomography (CT)/magnetic resonance imaging (MRI) can be used infrequently.	weak	↑
In intermediate-risk patients, offer intensified follow-up, including chest and abdominal CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	weak	↑
In high-risk patients, include chest and abdominal CT/MRI scans in follow-up examinations.	weak	↑
Intensify follow-up in patients after NSS for tumours > 7 cm or in patients with a positive surgical margin.	weak	↑
Base risk stratification on pre-existing classification systems such as the University of California Los Angeles integrated staging system integrated risk assessment score (http://urology.ucla.edu/body.cfm?id=443).	strong	↑↑

UISS = University of California Los Angeles integrated staging system.

8.4 Research priorities

There is a clear need for future research to determine whether follow-up can optimise patient survival. Further information should be sought at what time point restaging has the highest chance to detect recurrence. Prognostic markers at surgery should be investigated to determine the risk of relapse over time.

9. REFERENCES

1. Ljungberg, B., *et al.* Renal cell carcinoma guideline. *Eur Urol*, 2007. 51: 1502.
<https://www.ncbi.nlm.nih.gov/pubmed/17408850>
2. Ljungberg, B., *et al.* EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol*, 2015. 67: 913.
<https://www.ncbi.nlm.nih.gov/pubmed/25616710>
3. Guyatt, G.H., *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 2008. 336: 924.
<https://www.ncbi.nlm.nih.gov/pubmed/18436948>
4. Guyatt, G.H., *et al.* What is "quality of evidence" and why is it important to clinicians? *BMJ*, 2008. 336: 995.
<https://www.ncbi.nlm.nih.gov/pubmed/18456631>
5. Guyatt, G.H., *et al.* Going from evidence to recommendations. *BMJ*, 2008. 336: 1049.
<https://www.ncbi.nlm.nih.gov/pubmed/18467413>
6. Vogel, T., *et al.* Imaging in Suspected Renal Cell Carcinoma: A Systematic Review. prior to print, 2017.
7. Marconi, L., *et al.* Systematic review of the best surgical treatment for clinical T2N0M0 Renal Cell Cancer PROSPERO International prospective register of systematic reviews, 2016. CRD42016036697.
<https://www.ncbi.nlm.nih.gov/pubmed/26707869>
8. Fernández-Pello, S., *et al.* A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma. *Eur Urol*, 2017. 71: 426.
<https://www.ncbi.nlm.nih.gov/pubmed/27939075>
9. European Network of Cancer Registries: Eurocim version 4.0. 2001: Lyon, France.
10. Lindblad, P. Epidemiology of renal cell carcinoma. *Scand J Surg*, 2004. 93: 88.
<https://www.ncbi.nlm.nih.gov/pubmed/15285559>
11. Ferlay, J., *et al.* Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*, 2013. 49: 1374.
<https://www.ncbi.nlm.nih.gov/pubmed/23485231>
12. Levi, F., *et al.* The changing pattern of kidney cancer incidence and mortality in Europe. *BJU Int*, 2008. 101: 949.
<https://www.ncbi.nlm.nih.gov/pubmed/18241251>
13. King, S.C., *et al.* Continued increase in incidence of renal cell carcinoma, especially in young patients and high grade disease: United States 2001 to 2010. *J Urol*, 2014. 191: 1665.
<https://www.ncbi.nlm.nih.gov/pubmed/24423441>
14. Bergstrom, A., *et al.* Obesity and renal cell cancer--a quantitative review. *Br J Cancer*, 2001. 85: 984.
<https://www.ncbi.nlm.nih.gov/pubmed/11592770>
15. Clague, J., *et al.* Family history and risk of renal cell carcinoma: results from a case-control study and systematic meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 2009. 18: 801.
<https://www.ncbi.nlm.nih.gov/pubmed/19240244>
16. Choueiri, T.K., *et al.* Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies. *Int J Cancer*, 2014. 134: 384.
<https://www.ncbi.nlm.nih.gov/pubmed/23400756>
17. Liu, B., *et al.* Cruciferous vegetables consumption and risk of renal cell carcinoma: a meta-analysis. *Nutr Cancer*, 2013. 65: 668.
<https://www.ncbi.nlm.nih.gov/pubmed/23859034>
18. Cheungpasitporn, W., *et al.* The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis. *QJM*, 2015. 108: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/25208892>
19. Gonzalez, H.C., *et al.* Chronic hepatitis C infection as a risk factor for renal cell carcinoma. *Dig Dis Sci*, 2015. 60: 1820.
<https://www.ncbi.nlm.nih.gov/pubmed/25592719>
20. Macleod, L.C., *et al.* Risk factors for renal cell carcinoma in the VITAL study. *J Urol*, 2013. 190: 1657.
<https://www.ncbi.nlm.nih.gov/pubmed/23665301>
21. Lipworth, L., *et al.* The epidemiology of renal cell carcinoma. *J Urol*, 2006. 176: 2353.
<https://www.ncbi.nlm.nih.gov/pubmed/17085101>
22. International Agency for Research on cancer (IARC). WHO IARC monographs. 2004. 83.
<http://monographs.iarc.fr/ENG/Monographs/PDFs/>

23. Weikert, S., *et al.* Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. *Am J Epidemiol*, 2008. 167: 438.
<https://www.ncbi.nlm.nih.gov/pubmed/18048375>
24. Daniel, C.R., *et al.* Large prospective investigation of meat intake, related mutagens, and risk of renal cell carcinoma. *Am J Clin Nutr*, 2012. 95: 155.
<https://www.ncbi.nlm.nih.gov/pubmed/22170360>
25. Weikert, S., *et al.* Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer*, 2006. 118: 3133.
<https://www.ncbi.nlm.nih.gov/pubmed/16425278>
26. Rohrmann, S., *et al.* Meat and fish consumption and the risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. *Int J Cancer*, 2015. 136: E423.
<https://www.ncbi.nlm.nih.gov/pubmed/25258006>
27. Bellocco, R., *et al.* Alcohol drinking and risk of renal cell carcinoma: results of a meta-analysis. *Ann Oncol*, 2012. 23: 2235.
<https://www.ncbi.nlm.nih.gov/pubmed/22398178>
28. Song, D.Y., *et al.* Alcohol intake and renal cell cancer risk: a meta-analysis. *Br J Cancer*, 2012. 106: 1881.
<https://www.ncbi.nlm.nih.gov/pubmed/22516951>
29. Patard, J.J., *et al.* Prognostic significance of the mode of detection in renal tumours. *BJU Int*, 2002. 90: 358.
<https://www.ncbi.nlm.nih.gov/pubmed/12175389>
30. Kato, M., *et al.* Natural history of small renal cell carcinoma: evaluation of growth rate, histological grade, cell proliferation and apoptosis. *J Urol*, 2004. 172: 863.
<https://www.ncbi.nlm.nih.gov/pubmed/15310984>
31. Tsui, K.H., *et al.* Renal cell carcinoma: prognostic significance of incidentally detected tumors. *J Urol*, 2000. 163: 426.
<https://www.ncbi.nlm.nih.gov/pubmed/10647646>
32. Moch, H., *et al.* The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol*, 2016. 70: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/26935559>
33. Moch, H., *et al.* IARC WHO Classification of Tumours, No 8. WHO Classification of Tumours of the Urinary System and Male Genital Organs. Fourth edition. 2016, Lyon, France.
<http://apps.who.int/bookorders/anglais/detart1.jsp?codlan=1&codcol=70&codcch=4008>
34. Brugarolas, J. Molecular genetics of clear-cell renal cell carcinoma. *J Clin Oncol*, 2014. 32: 1968.
<https://www.ncbi.nlm.nih.gov/pubmed/24821879>
35. Capitanio, U., *et al.* A critical assessment of the prognostic value of clear cell, papillary and chromophobe histological subtypes in renal cell carcinoma: a population-based study. *BJU Int*, 2009. 103: 1496.
<https://www.ncbi.nlm.nih.gov/pubmed/19076149>
36. Keegan, K.A., *et al.* Histopathology of surgically treated renal cell carcinoma: survival differences by subtype and stage. *J Urol*, 2012. 188: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/22698625>
37. Beck, S.D., *et al.* Effect of papillary and chromophobe cell type on disease-free survival after nephrectomy for renal cell carcinoma. *Ann Surg Oncol*, 2004. 11: 71.
<https://www.ncbi.nlm.nih.gov/pubmed/14699037>
38. Tsui, K.H., *et al.* Prognostic indicators for renal cell carcinoma: a multivariate analysis of 643 patients using the revised 1997 TNM staging criteria. *J Urol*, 2000. 163: 1090.
<https://www.ncbi.nlm.nih.gov/pubmed/10737472>
39. Linehan, W.M., *et al.* Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N Engl J Med*, 2016. 374: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/26536169>
40. Steffens, S., *et al.* Incidence and long-term prognosis of papillary compared to clear cell renal cell carcinoma--a multicentre study. *Eur J Cancer*, 2012. 48: 2347.
<https://www.ncbi.nlm.nih.gov/pubmed/22698386>
41. Ledezma, R.A., *et al.* Clinically localized type 1 and 2 papillary renal cell carcinomas have similar survival outcomes following surgery. *World J Urol*, 2016. 34: 687.
<https://www.ncbi.nlm.nih.gov/pubmed/26407582>
42. Urge, T., *et al.* Typical signs of oncocytic papillary renal cell carcinoma in everyday clinical praxis. *World J Urol*, 2010. 28: 513.
<https://www.ncbi.nlm.nih.gov/pubmed/20454896>

43. Volpe, A., *et al.* Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. *BJU Int*, 2012. 110: 76.
<https://www.ncbi.nlm.nih.gov/pubmed/22044519>
44. Hora, M., *et al.* Tumours in end-stage kidney. *Transplant Proc*, 2008. 40: 3354.
<https://www.ncbi.nlm.nih.gov/pubmed/19100388>
45. Neuzillet, Y., *et al.* Renal cell carcinoma (RCC) in patients with end-stage renal disease exhibits many favourable clinical, pathologic, and outcome features compared with RCC in the general population. *Eur Urol*, 2011. 60: 366.
<https://www.ncbi.nlm.nih.gov/pubmed/21377780>
46. Srigley, J.R., *et al.* Uncommon and recently described renal carcinomas. *Mod Pathol*, 2009. 22 Suppl 2: S2.
<https://www.ncbi.nlm.nih.gov/pubmed/19494850>
47. Srigley, J.R., *et al.* The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *Am J Surg Pathol*, 2013. 37: 1469.
<https://www.ncbi.nlm.nih.gov/pubmed/24025519>
48. Eble JN, *et al.* Pathology and genetics of tumours of the urinary system and male genital organs. World Health Organization Classification of Tumours., in Pathology and genetics of tumours of the urinary system and male genital organs. 2004, IARC: Lyon.
49. Shuch, B., *et al.* Defining early-onset kidney cancer: implications for germline and somatic mutation testing and clinical management. *J Clin Oncol*, 2014. 32: 431.
<https://www.ncbi.nlm.nih.gov/pubmed/24378414>
50. Pignot, G., *et al.* Survival analysis of 130 patients with papillary renal cell carcinoma: prognostic utility of type 1 and type 2 subclassification. *Urology*, 2007. 69: 230.
<https://www.ncbi.nlm.nih.gov/pubmed/17275070>
51. Przybycin, C.G., *et al.* Hereditary syndromes with associated renal neoplasia: a practical guide to histologic recognition in renal tumor resection specimens. *Adv Anat Pathol*, 2013. 20: 245.
<https://www.ncbi.nlm.nih.gov/pubmed/23752087>
52. Shuch, B., *et al.* The surgical approach to multifocal renal cancers: hereditary syndromes, ipsilateral multifocality, and bilateral tumors. *Urol Clin North Am*, 2012. 39: 133.
<https://www.ncbi.nlm.nih.gov/pubmed/22487757>
53. Bratslavsky, G., *et al.* Salvage partial nephrectomy for hereditary renal cancer: feasibility and outcomes. *J Urol*, 2008. 179: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/17997447>
54. Grubb, R.L., 3rd, *et al.* Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. *J Urol*, 2007. 177: 2074.
<https://www.ncbi.nlm.nih.gov/pubmed/17509289>
55. Nielsen, S.M., *et al.* Von Hippel-Lindau Disease: Genetics and Role of Genetic Counseling in a Multiple Neoplasia Syndrome. *J Clin Oncol*, 2016. 34: 2172.
<https://www.ncbi.nlm.nih.gov/pubmed/27114602>
56. Kauffman, E.C., *et al.* Molecular genetics and cellular features of TFE3 and TFEB fusion kidney cancers. *Nat Rev Urol*, 2014. 11: 465.
<https://www.ncbi.nlm.nih.gov/pubmed/25048860>
57. Bhatt, J.R., *et al.* Natural History of Renal Angiomyolipoma (AML): Most Patients with Large AMLs >4cm Can Be Offered Active Surveillance as an Initial Management Strategy. *Eur Urol*, 2016. 70: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/26873836>
58. Nese, N., *et al.* Pure epithelioid PEComas (so-called epithelioid angiomyolipoma) of the kidney: A clinicopathologic study of 41 cases: detailed assessment of morphology and risk stratification. *Am J Surg Pathol*, 2011. 35: 161.
<https://www.ncbi.nlm.nih.gov/pubmed/21263237>
59. Mues, A.C., *et al.* Contemporary experience in the management of angiomyolipoma. *J Endourol*, 2010. 24: 1883.
<https://www.ncbi.nlm.nih.gov/pubmed/20919915>
60. Ramon, J., *et al.* Renal angiomyolipoma: long-term results following selective arterial embolization. *Eur Urol*, 2009. 55: 1155.
<https://www.ncbi.nlm.nih.gov/pubmed/18440125>
61. Nelson, C.P., *et al.* Contemporary diagnosis and management of renal angiomyolipoma. *J Urol*, 2002. 168: 1315.
<https://www.ncbi.nlm.nih.gov/pubmed/12352384>

62. Uzaid, I., *et al.* Active surveillance for renal angiomyolipoma: outcomes and factors predictive of delayed intervention. *BJU Int*, 2014. 114: 412.
<https://www.ncbi.nlm.nih.gov/pubmed/24325283>
63. Hocquelet, A., *et al.* Long-term results of preventive embolization of renal angiomyolipomas: evaluation of predictive factors of volume decrease. *Eur Radiol*, 2014. 24: 1785.
<https://www.ncbi.nlm.nih.gov/pubmed/24889998>
64. Choueiri, T.K., *et al.* Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*, 2015. 373: 1814.
<https://www.ncbi.nlm.nih.gov/pubmed/Choueiri>
65. Murray, T.E., *et al.* Transarterial Embolization of Angiomyolipoma: A Systematic Review. *J Urol*, 2015. 194: 635.
<https://www.ncbi.nlm.nih.gov/pubmed/25916674>
66. Castle, S.M., *et al.* Radiofrequency ablation (RFA) therapy for renal angiomyolipoma (AML): an alternative to angio-embolization and nephron-sparing surgery. *BJU Int*, 2012. 109: 384.
<https://www.ncbi.nlm.nih.gov/pubmed/22176671>
67. Bissler, J.J., *et al.* Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangiomyomatosis: extension of a randomized controlled trial. *Nephrol Dial Transplant*, 2016. 31: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/26156073>
68. Staehler, M., *et al.* Nephron-sparing resection of angiomyolipoma after sirolimus pretreatment in patients with tuberous sclerosis. *Int Urol Nephrol*, 2012. 44: 1657.
<https://www.ncbi.nlm.nih.gov/pubmed/23054313>
69. Roubaud, G., *et al.* Combination of gemcitabine and doxorubicin in rapidly progressive metastatic renal cell carcinoma and/or sarcomatoid renal cell carcinoma. *Oncology*, 2011. 80: 214.
<https://www.ncbi.nlm.nih.gov/pubmed/21720184>
70. Abern, M.R., *et al.* Characteristics and outcomes of tumors arising from the distal nephron. *Urology*, 2012. 80: 140.
<https://www.ncbi.nlm.nih.gov/pubmed/22626576>
71. Husillos, A., *et al.* [Collecting duct renal cell carcinoma]. *Actas Urol Esp*, 2011. 35: 368.
<https://www.ncbi.nlm.nih.gov/pubmed/21450372>
72. Hora, M., *et al.* MiT translocation renal cell carcinomas: two subgroups of tumours with translocations involving 6p21 [t (6; 11)] and Xp11.2 [t (X;1 or X or 17)]. Springerplus, 2014. 3: 245.
<https://www.ncbi.nlm.nih.gov/pubmed/24877033>
73. Choudhary, S., *et al.* Renal oncocytoma: CT features cannot reliably distinguish oncocytoma from other renal neoplasms. *Clin Radiol*, 2009. 64: 517.
<https://www.ncbi.nlm.nih.gov/pubmed/19348848>
74. Bird, V.G., *et al.* Differentiation of oncocytoma and renal cell carcinoma in small renal masses (<4 cm): the role of 4-phase computerized tomography. *World J Urol*, 2011. 29: 787.
<https://www.ncbi.nlm.nih.gov/pubmed/20717829>
75. Kurup, A.N., *et al.* Renal oncocytoma growth rates before intervention. *BJU Int*, 2012. 110: 1444.
<https://www.ncbi.nlm.nih.gov/pubmed/22520366>
76. Kawaguchi, S., *et al.* Most renal oncocytomas appear to grow: observations of tumor kinetics with active surveillance. *J Urol*, 2011. 186: 1218.
<https://www.ncbi.nlm.nih.gov/pubmed/21849182>
77. Richard, P.O., *et al.* Active Surveillance for Renal Neoplasms with Oncocytic Features is Safe. *J Urol*, 2016. 195: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/26388501>
78. Brierley, J.D., *et al.*, TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. Wiley-Blackwell, 2017. 199.
<http://www.uicc.org/tnm>
79. Gospodarowicz, M.K., *et al.* The process for continuous improvement of the TNM classification. *Cancer*, 2004. 100: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/14692017>
80. Kim, S.P., *et al.* Independent validation of the 2010 American Joint Committee on Cancer TNM classification for renal cell carcinoma: results from a large, single institution cohort. *J Urol*, 2011. 185: 2035.
<https://www.ncbi.nlm.nih.gov/pubmed/21496854>
81. Novara, G., *et al.* Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? *Eur Urol*, 2010. 58: 588.
<https://www.ncbi.nlm.nih.gov/pubmed/20674150>

82. Waalkes, S., *et al.* Is there a need to further subclassify pT2 renal cell cancers as implemented by the revised 7th TNM version? *Eur Urol*, 2011. 59: 258.
<https://www.ncbi.nlm.nih.gov/pubmed/21030143>
83. Bertini, R., *et al.* Renal sinus fat invasion in pT3a clear cell renal cell carcinoma affects outcomes of patients without nodal involvement or distant metastases. *J Urol*, 2009. 181: 2027.
<https://www.ncbi.nlm.nih.gov/pubmed/19286201>
84. Poon, S.A., *et al.* Invasion of renal sinus fat is not an independent predictor of survival in pT3a renal cell carcinoma. *BJU Int*, 2009. 103: 1622.
<https://www.ncbi.nlm.nih.gov/pubmed/19154464>
85. Bedke, J., *et al.* Perinephric and renal sinus fat infiltration in pT3a renal cell carcinoma: possible prognostic differences. *BJU Int*, 2009. 103: 1349.
<https://www.ncbi.nlm.nih.gov/pubmed/19076147>
86. Heidenreich, A., *et al.* Preoperative imaging in renal cell cancer. *World J Urol*, 2004. 22: 307.
<https://www.ncbi.nlm.nih.gov/pubmed/15290202>
87. Sheth, S., *et al.* Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector ct and three-dimensional CT. *Radiographics*, 2001. 21 Spec No: S237.
<https://www.ncbi.nlm.nih.gov/pubmed/11598260>
88. Wittekind B.J, C. Compton CC, Sobin LH (eds). A Commentary on Uniform Use. UICC International Union against cancer. 4th edition. Wiley-Blackwell. 106.
<http://eu.wiley.com/WileyCDA/WileyTitle/productCd-1444332430.html>
89. Klatte, T., *et al.* A Literature Review of Renal Surgical Anatomy and Surgical Strategies for Partial Nephrectomy. *Eur Urol*, 2015. 68: 980.
<https://www.ncbi.nlm.nih.gov/pubmed/25911061>
90. Spaliviero, M., *et al.* An Arterial Based Complexity (ABC) Scoring System to Assess the Morbidity Profile of Partial Nephrectomy. *Eur Urol*, 2016. 69: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/26298208>
91. Hakky, T.S., *et al.* Zonal NePhRO scoring system: a superior renal tumor complexity classification model. *Clin Genitourin Cancer*, 2014. 12: e13.
<https://www.ncbi.nlm.nih.gov/pubmed/24120084>
92. Jayson, M., *et al.* Increased incidence of serendipitously discovered renal cell carcinoma. *Urology*, 1998. 51: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/9495698>
93. Lee, C.T., *et al.* Mode of presentation of renal cell carcinoma provides prognostic information. *Urol Oncol*, 2002. 7: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/12474528>
94. Patard, J.J., *et al.* Correlation between symptom graduation, tumor characteristics and survival in renal cell carcinoma. *Eur Urol*, 2003. 44: 226.
<https://www.ncbi.nlm.nih.gov/pubmed/12875943>
95. Kim, H.L., *et al.* Paraneoplastic signs and symptoms of renal cell carcinoma: implications for prognosis. *J Urol*, 2003. 170: 1742.
<https://www.ncbi.nlm.nih.gov/pubmed/14532767>
96. Magera, J.S., Jr., *et al.* Association of abnormal preoperative laboratory values with survival after radical nephrectomy for clinically confined clear cell renal cell carcinoma. *Urology*, 2008. 71: 278.
<https://www.ncbi.nlm.nih.gov/pubmed/18308103>
97. Uzzo, R.G., *et al.* Nephron sparing surgery for renal tumors: indications, techniques and outcomes. *J Urol*, 2001. 166: 6.
<https://www.ncbi.nlm.nih.gov/pubmed/11435813>
98. Huang, W.C., *et al.* Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol*, 2006. 7: 735.
<https://www.ncbi.nlm.nih.gov/pubmed/16945768>
99. Israel, G.M., *et al.* How I do it: evaluating renal masses. *Radiology*, 2005. 236: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/16040900>
100. Fan, L., *et al.* Diagnostic efficacy of contrast-enhanced ultrasonography in solid renal parenchymal lesions with maximum diameters of 5 cm. *J Ultrasound Med*, 2008. 27: 875.
<https://www.ncbi.nlm.nih.gov/pubmed/18499847>
101. Correas, J.M., *et al.* [Guidelines for contrast enhanced ultrasound (CEUS)--update 2008]. *J Radiol*, 2009. 90: 123.
<https://www.ncbi.nlm.nih.gov/pubmed/19212280>

102. Mitterberger, M., *et al.* Contrast-enhanced ultrasound for diagnosis of prostate cancer and kidney lesions. *Eur J Radiol*, 2007. 64: 231.
<https://www.ncbi.nlm.nih.gov/pubmed/17881175>
103. Israel, G.M., *et al.* Pitfalls in renal mass evaluation and how to avoid them. *Radiographics*, 2008. 28: 1325.
<https://www.ncbi.nlm.nih.gov/pubmed/18794310>
104. Rosenkrantz, A.B., *et al.* MRI features of renal oncocytoma and chromophobe renal cell carcinoma. *AJR Am J Roentgenol*, 2010. 195: W421.
<https://www.ncbi.nlm.nih.gov/pubmed/21098174>
105. Hindman, N., *et al.* Angiomyolipoma with minimal fat: can it be differentiated from clear cell renal cell carcinoma by using standard MR techniques? *Radiology*, 2012. 265: 468.
<https://www.ncbi.nlm.nih.gov/pubmed/23012463>
106. Pedrosa, I., *et al.* MR imaging of renal masses: correlation with findings at surgery and pathologic analysis. *Radiographics*, 2008. 28: 985.
<https://www.ncbi.nlm.nih.gov/pubmed/18635625>
107. Sokhi, H.K., *et al.* Stage T3a renal cell carcinoma: staging accuracy of CT for sinus fat, perinephric fat or renal vein invasion. *Br J Radiol*, 2015. 88: 20140504.
<https://www.ncbi.nlm.nih.gov/pubmed/25410425>
108. Gong, I.H., *et al.* Relationship among total kidney volume, renal function and age. *J Urol*, 2012. 187: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/22099987>
109. Ferda, J., *et al.* Assessment of the kidney tumor vascular supply by two-phase MDCT-angiography. *Eur J Radiol*, 2007. 62: 295.
<https://www.ncbi.nlm.nih.gov/pubmed/17324548>
110. Shao, P., *et al.* Precise segmental renal artery clamping under the guidance of dual-source computed tomography angiography during laparoscopic partial nephrectomy. *Eur Urol*, 2012. 62: 1001.
<https://www.ncbi.nlm.nih.gov/pubmed/22695243>
111. Janus, C.L., *et al.* Comparison of MRI and CT for study of renal and perirenal masses. *Crit Rev Diagn Imaging*, 1991. 32: 69.
<https://www.ncbi.nlm.nih.gov/pubmed/1863349>
112. Krestin, G.P., *et al.* [The importance of magnetic resonance tomography in the diagnosis and staging of renal cell carcinoma]. *Radiologe*, 1992. 32: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/1565792>
113. Mueller-Lisse, U.G., *et al.* Imaging of advanced renal cell carcinoma. *World J Urol*, 2010. 28: 253.
<https://www.ncbi.nlm.nih.gov/pubmed/20458484>
114. Kabala, J.E., *et al.* Magnetic resonance imaging in the staging of renal cell carcinoma. *Br J Radiol*, 1991. 64: 683.
<https://www.ncbi.nlm.nih.gov/pubmed/1884119>
115. Putra, L.G., *et al.* Improved assessment of renal lesions in pregnancy with magnetic resonance imaging. *Urology*, 2009. 74: 535.
<https://www.ncbi.nlm.nih.gov/pubmed/19604560>
116. Giannarini, G., *et al.* Potential and limitations of diffusion-weighted magnetic resonance imaging in kidney, prostate, and bladder cancer including pelvic lymph node staging: a critical analysis of the literature. *Eur Urol*, 2012. 61: 326.
<https://www.ncbi.nlm.nih.gov/pubmed/22000497>
117. Park, J.W., *et al.* Significance of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for the postoperative surveillance of advanced renal cell carcinoma. *BJU Int*, 2009. 103: 615.
<https://www.ncbi.nlm.nih.gov/pubmed/19007371>
118. Bechtold, R.E., *et al.* Imaging approach to staging of renal cell carcinoma. *Urol Clin North Am*, 1997. 24: 507.
<https://www.ncbi.nlm.nih.gov/pubmed/9275976>
119. Miles, K.A., *et al.* CT staging of renal carcinoma: a prospective comparison of three dynamic computed tomography techniques. *Eur J Radiol*, 1991. 13: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/1889427>
120. Lim, D.J., *et al.* Computerized tomography in the preoperative staging for pulmonary metastases in patients with renal cell carcinoma. *J Urol*, 1993. 150: 1112.
<https://www.ncbi.nlm.nih.gov/pubmed/8371366>

121. Marshall, M.E., *et al.* Low incidence of asymptomatic brain metastases in patients with renal cell carcinoma. *Urology*, 1990. 36: 300.
<https://www.ncbi.nlm.nih.gov/pubmed/2219605>
122. Koga, S., *et al.* The diagnostic value of bone scan in patients with renal cell carcinoma. *J Urol*, 2001. 166: 2126.
<https://www.ncbi.nlm.nih.gov/pubmed/11696720>
123. Henriksson, C., *et al.* Skeletal metastases in 102 patients evaluated before surgery for renal cell carcinoma. *Scand J Urol Nephrol*, 1992. 26: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/1292074>
124. Seaman, E., *et al.* Association of radionuclide bone scan and serum alkaline phosphatase in patients with metastatic renal cell carcinoma. *Urology*, 1996. 48: 692.
<https://www.ncbi.nlm.nih.gov/pubmed/8911510>
125. Warren, K.S., *et al.* The Bosniak classification of renal cystic masses. *BJU Int*, 2005. 95: 939.
<https://www.ncbi.nlm.nih.gov/pubmed/15839908>
126. Bosniak, M.A. The use of the Bosniak classification system for renal cysts and cystic tumors. *J Urol*, 1997. 157: 1852.
<https://www.ncbi.nlm.nih.gov/pubmed/9112545>
127. Richard, P.O., *et al.* Renal Tumor Biopsy for Small Renal Masses: A Single-center 13-year Experience. *Eur Urol*, 2015. 68: 1007.
<https://www.ncbi.nlm.nih.gov/pubmed/25900781>
128. Shannon, B.A., *et al.* The value of preoperative needle core biopsy for diagnosing benign lesions among small, incidentally detected renal masses. *J Urol*, 2008. 180: 1257.
<https://www.ncbi.nlm.nih.gov/pubmed/18707712>
129. Maturen, K.E., *et al.* Renal mass core biopsy: accuracy and impact on clinical management. *AJR Am J Roentgenol*, 2007. 188: 563.
<https://www.ncbi.nlm.nih.gov/pubmed/17242269>
130. Volpe, A., *et al.* Contemporary results of percutaneous biopsy of 100 small renal masses: a single center experience. *J Urol*, 2008. 180: 2333.
<https://www.ncbi.nlm.nih.gov/pubmed/18930274>
131. Veltri, A., *et al.* Diagnostic accuracy and clinical impact of imaging-guided needle biopsy of renal masses. Retrospective analysis on 150 cases. *Eur Radiol*, 2011. 21: 393.
<https://www.ncbi.nlm.nih.gov/pubmed/20809129>
132. Abel, E.J., *et al.* Percutaneous biopsy of primary tumor in metastatic renal cell carcinoma to predict high risk pathological features: comparison with nephrectomy assessment. *J Urol*, 2010. 184: 1877.
<https://www.ncbi.nlm.nih.gov/pubmed/20850148>
133. Leveridge, M.J., *et al.* Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. *Eur Urol*, 2011. 60: 578.
<https://www.ncbi.nlm.nih.gov/pubmed/21704449>
134. Breda, A., *et al.* Comparison of accuracy of 14-, 18- and 20-G needles in ex-vivo renal mass biopsy: a prospective, blinded study. *BJU Int*, 2010. 105: 940.
<https://www.ncbi.nlm.nih.gov/pubmed/19888984>
135. Marconi, L., *et al.* Systematic Review and Meta-analysis of Diagnostic Accuracy of Percutaneous Renal Tumour Biopsy. *Eur Urol*, 2016. 69: 660.
<https://www.ncbi.nlm.nih.gov/pubmed/26323946>
136. Motzer, R.J., *et al.* Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 2014. 32: 2765.
<https://www.ncbi.nlm.nih.gov/pubmed/25049330>
137. Wood, B.J., *et al.* Imaging guided biopsy of renal masses: indications, accuracy and impact on clinical management. *J Urol*, 1999. 161: 1470.
<https://www.ncbi.nlm.nih.gov/pubmed/10210375>
138. Somani, B.K., *et al.* Image-guided biopsy-diagnosed renal cell carcinoma: critical appraisal of technique and long-term follow-up. *Eur Urol*, 2007. 51: 1289.
<https://www.ncbi.nlm.nih.gov/pubmed/17081679>
139. Vasudevan, A., *et al.* Incidental renal tumours: the frequency of benign lesions and the role of preoperative core biopsy. *BJU Int*, 2006. 97: 946.
<https://www.ncbi.nlm.nih.gov/pubmed/16643475>
140. Neuzillet, Y., *et al.* Accuracy and clinical role of fine needle percutaneous biopsy with computerized tomography guidance of small (less than 4.0 cm) renal masses. *J Urol*, 2004. 171: 1802.
<https://www.ncbi.nlm.nih.gov/pubmed/15076280>

141. Schmidbauer, J., *et al.* Diagnostic accuracy of computed tomography-guided percutaneous biopsy of renal masses. *Eur Urol*, 2008. 53: 1003.
<https://www.ncbi.nlm.nih.gov/pubmed/18061339>
142. Wunderlich, H., *et al.* The accuracy of 250 fine needle biopsies of renal tumors. *J Urol*, 2005. 174: 44.
<https://www.ncbi.nlm.nih.gov/pubmed/15947574>
143. Abel, E.J., *et al.* Multi-Quadrant Biopsy Technique Improves Diagnostic Ability in Large Heterogeneous Renal Masses. *J Urol*, 2015. 194: 886.
<https://www.ncbi.nlm.nih.gov/pubmed/25837535>
144. Harisinghani, M.G., *et al.* Incidence of malignancy in complex cystic renal masses (Bosniak category III): should imaging-guided biopsy precede surgery? *AJR Am J Roentgenol*, 2003. 180: 755.
<https://www.ncbi.nlm.nih.gov/pubmed/12591691>
145. Lang, E.K., *et al.* CT-guided biopsy of indeterminate renal cystic masses (Bosniak 3 and 2F): accuracy and impact on clinical management. *Eur Radiol*, 2002. 12: 2518.
<https://www.ncbi.nlm.nih.gov/pubmed/12271393>
146. Sun, M., *et al.* Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. *Eur Urol*, 2011. 60: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/21741163>
147. Fuhrman, S.A., *et al.* Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol*, 1982. 6: 655.
<https://www.ncbi.nlm.nih.gov/pubmed/7180965>
148. Lang, H., *et al.* Multicenter determination of optimal interobserver agreement using the Fuhrman grading system for renal cell carcinoma: Assessment of 241 patients with > 15-year follow-up. *Cancer*, 2005. 103: 625.
<https://www.ncbi.nlm.nih.gov/pubmed/15611969>
149. Rioux-Leclercq, N., *et al.* Prognostic ability of simplified nuclear grading of renal cell carcinoma. *Cancer*, 2007. 109: 868.
<https://www.ncbi.nlm.nih.gov/pubmed/17262800>
150. Sun, M., *et al.* A proposal for reclassification of the Fuhrman grading system in patients with clear cell renal cell carcinoma. *Eur Urol*, 2009. 56: 775.
<https://www.ncbi.nlm.nih.gov/pubmed/19573980>
151. Delahunt, B., *et al.* The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol*, 2013. 37: 1490.
<https://www.ncbi.nlm.nih.gov/pubmed/24025520>
152. Cheville, J.C., *et al.* Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. *Am J Surg Pathol*, 2003. 27: 612.
<https://www.ncbi.nlm.nih.gov/pubmed/12717246>
153. Patard, J.J., *et al.* Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol*, 2005. 23: 2763.
<https://www.ncbi.nlm.nih.gov/pubmed/15837991>
154. Leibovich, B.C., *et al.* Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. *J Urol*, 2010. 183: 1309.
<https://www.ncbi.nlm.nih.gov/pubmed/20171681>
155. Linehan, W.M., *et al.* Genetic basis of cancer of the kidney: disease-specific approaches to therapy. *Clin Cancer Res*, 2004. 10: 6282S.
<https://www.ncbi.nlm.nih.gov/pubmed/15448018>
156. Wahlgren, T., *et al.* Treatment and overall survival in renal cell carcinoma: a Swedish population-based study (2000-2008). *Br J Cancer*, 2013. 108: 1541.
<https://www.ncbi.nlm.nih.gov/pubmed/23531701>
157. Li, P., *et al.* Survival among patients with advanced renal cell carcinoma in the pretargeted versus targeted therapy eras. *Cancer Med*, 2016. 5: 169.
<https://www.ncbi.nlm.nih.gov/pubmed/26645975>
158. Delahunt, B., *et al.* Morphologic typing of papillary renal cell carcinoma: comparison of growth kinetics and patient survival in 66 cases. *Hum Pathol*, 2001. 32: 590.
<https://www.ncbi.nlm.nih.gov/pubmed/11431713>
159. Klatte, T., *et al.* Renal cell carcinoma associated with transcription factor E3 expression and Xp11.2 translocation: incidence, characteristics, and prognosis. *Am J Clin Pathol*, 2012. 137: 761.
<https://www.ncbi.nlm.nih.gov/pubmed/22523215>

160. Yang, X.J., *et al.* A molecular classification of papillary renal cell carcinoma. *Cancer Res*, 2005. 65: 5628.
<https://www.ncbi.nlm.nih.gov/pubmed/15994935>
161. Furge, K.A., *et al.* Identification of deregulated oncogenic pathways in renal cell carcinoma: an integrated oncogenomic approach based on gene expression profiling. *Oncogene*, 2007. 26: 1346.
<https://www.ncbi.nlm.nih.gov/pubmed/17322920>
162. Haas, N.B., *et al.* Initial results from ASSURE (E2805): Adjuvant sorafenib or sunitinib for unfavorable renal carcinoma, an ECOG-ACRIN-led, NCTN phase III trial. *ASCO Meeting Abstracts*, 2015. 33: 403.
<http://meetinglibrary.asco.org/content/141765-159>
163. Bensalah, K., *et al.* Prognostic value of thrombocytosis in renal cell carcinoma. *J Urol*, 2006. 175: 859.
<https://www.ncbi.nlm.nih.gov/pubmed/16469566>
164. Kim, H.L., *et al.* Cachexia-like symptoms predict a worse prognosis in localized t1 renal cell carcinoma. *J Urol*, 2004. 171: 1810.
<https://www.ncbi.nlm.nih.gov/pubmed/15076282>
165. Patard, J.J., *et al.* Multi-institutional validation of a symptom based classification for renal cell carcinoma. *J Urol*, 2004. 172: 858.
<https://www.ncbi.nlm.nih.gov/pubmed/15310983>
166. Cho, D.S., *et al.* Prognostic significance of modified Glasgow Prognostic Score in patients with non-metastatic clear cell renal cell carcinoma. *Scand J Urol*, 2016. 50: 186.
<https://www.ncbi.nlm.nih.gov/pubmed/26878156>
167. A Phase 3, Randomized, Open-Label Study of Nivolumab Combined With Ipilimumab Versus Sunitinib Monotherapy in Subjects With Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma. 2015 p. NCT02231749.
<https://clinicaltrials.gov/ct2/show/NCT02231749>
168. Sim, S.H., *et al.* Prognostic utility of pre-operative circulating osteopontin, carbonic anhydrase IX and CRP in renal cell carcinoma. *Br J Cancer*, 2012. 107: 1131.
<https://www.ncbi.nlm.nih.gov/pubmed/22918393>
169. Sabatino, M., *et al.* Serum vascular endothelial growth factor and fibronectin predict clinical response to high-dose interleukin-2 therapy. *J Clin Oncol*, 2009. 27: 2645.
<https://www.ncbi.nlm.nih.gov/pubmed/19364969>
170. Li, G., *et al.* Serum carbonic anhydrase 9 level is associated with postoperative recurrence of conventional renal cell cancer. *J Urol*, 2008. 180: 510.
<https://www.ncbi.nlm.nih.gov/pubmed/18550116>
171. Choueiri, T.K., *et al.* A phase I study of cabozantinib (XL184) in patients with renal cell cancer. *Ann Oncol*, 2014. 25: 1603.
<https://www.ncbi.nlm.nih.gov/pubmed/24827131>
172. Motzer, R.J., *et al.* Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*, 2015. 373: 1803.
<https://www.ncbi.nlm.nih.gov/pubmed/26406148>
173. Minardi, D., *et al.* Loss of nuclear BAP1 protein expression is a marker of poor prognosis in patients with clear cell renal cell carcinoma. *Urol Oncol*, 2016. 34: 338 e11.
<https://www.ncbi.nlm.nih.gov/pubmed/27085487>
174. Kapur, P., *et al.* Effects on survival of BAP1 and PBRM1 mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation. *Lancet Oncol*, 2013. 14: 159.
<https://www.ncbi.nlm.nih.gov/pubmed/23333114>
175. Joseph, R.W., *et al.* Clear Cell Renal Cell Carcinoma Subtypes Identified by BAP1 and PBRM1 Expression. *J Urol*, 2016. 195: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/26300218>
176. Rini, B., *et al.* A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. *Lancet Oncol*, 2015. 16: 676.
<https://www.ncbi.nlm.nih.gov/pubmed/25979595>
177. Kohn, L., *et al.* Specific genomic aberrations predict survival, but low mutation rate in cancer hot spots, in clear cell renal cell carcinoma. *Appl Immunohistochem Mol Morphol*, 2015. 23: 334.
<https://www.ncbi.nlm.nih.gov/pubmed/24992170>
178. Wei, J.H., *et al.* A CpG-methylation-based assay to predict survival in clear cell renal cell carcinoma. *Nat Commun*, 2015. 6: 8699.
<https://www.ncbi.nlm.nih.gov/pubmed/26515236>

179. Sorbellini, M., *et al.* A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. *J Urol*, 2005. 173: 48.
<https://www.ncbi.nlm.nih.gov/pubmed/15592023>
180. Zisman, A., *et al.* Improved prognostication of renal cell carcinoma using an integrated staging system. *J Clin Oncol*, 2001. 19: 1649.
<https://www.ncbi.nlm.nih.gov/pubmed/11250993>
181. Frank, I., *et al.* An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol*, 2002. 168: 2395.
<https://www.ncbi.nlm.nih.gov/pubmed/12441925>
182. Leibovich, B.C., *et al.* Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer*, 2003. 97: 1663.
<https://www.ncbi.nlm.nih.gov/pubmed/12655523>
183. Patard, J.J., *et al.* Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. *J Clin Oncol*, 2004. 22: 3316.
<https://www.ncbi.nlm.nih.gov/pubmed/15310775>
184. Karakiewicz, P.I., *et al.* Multi-institutional validation of a new renal cancer-specific survival nomogram. *J Clin Oncol*, 2007. 25: 1316.
<https://www.ncbi.nlm.nih.gov/pubmed/17416852>
185. Zigeuner, R., *et al.* External validation of the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score for clear-cell renal cell carcinoma in a single European centre applying routine pathology. *Eur Urol*, 2010. 57: 102.
<https://www.ncbi.nlm.nih.gov/pubmed/18715700>
186. Isbarn, H., *et al.* Predicting cancer-control outcomes in patients with renal cell carcinoma. *Curr Opin Urol*, 2009. 19: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/19325492>
187. Raj, G.V., *et al.* Preoperative nomogram predicting 12-year probability of metastatic renal cancer. *J Urol*, 2008. 179: 2146.
<https://www.ncbi.nlm.nih.gov/pubmed/18423735>
188. Karakiewicz, P.I., *et al.* A preoperative prognostic model for patients treated with nephrectomy for renal cell carcinoma. *Eur Urol*, 2009. 55: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/18715700>
189. MacLennan, S., *et al.* Systematic review of perioperative and quality-of-life outcomes following surgical management of localised renal cancer. *Eur Urol*, 2012. 62: 1097.
<https://www.ncbi.nlm.nih.gov/pubmed/22841673>
190. MacLennan, S., *et al.* Systematic review of oncological outcomes following surgical management of localised renal cancer. *Eur Urol*, 2012. 61: 972.
<https://www.ncbi.nlm.nih.gov/pubmed/22405593>
191. Butler, B.P., *et al.* Management of small unilateral renal cell carcinomas: radical versus nephron-sparing surgery. *Urology*, 1995. 45: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/7817478>
192. Gratzke, C., *et al.* Quality of life and perioperative outcomes after retroperitoneoscopic radical nephrectomy (RN), open RN and nephron-sparing surgery in patients with renal cell carcinoma. *BJU Int*, 2009. 104: 470.
<https://www.ncbi.nlm.nih.gov/pubmed/19239445>
193. D'Armiento, M., *et al.* Elective conservative surgery for renal carcinoma versus radical nephrectomy: a prospective study. *Br J Urol*, 1997. 79: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/9043488>
194. Lee JH, *et al.* Comparison of the surgical outcome and renal function between radical and nephron-sparing surgery for renal cell carcinomas. *Korean J Urol*, 2007: 671.
http://www.koreascience.or.kr/article/ArticleFullRecord.jsp?cn=BNGGBM_2007_v48n7_671
195. Van Poppel, H., *et al.* A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol*, 2011. 59: 543.
<https://www.ncbi.nlm.nih.gov/pubmed/21186077>
196. Huang, W.C., *et al.* Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? *J Urol*, 2009. 181: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/19012918>

197. Kates, M., *et al.* Increased risk of overall and cardiovascular mortality after radical nephrectomy for renal cell carcinoma 2 cm or less. *J Urol*, 2011. 186: 1247.
<https://www.ncbi.nlm.nih.gov/pubmed/21849201>
198. Thompson, R.H., *et al.* Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol*, 2015. 67: 252.
<https://www.ncbi.nlm.nih.gov/pubmed/25108580>
199. Sun, M., *et al.* Management of localized kidney cancer: calculating cancer-specific mortality and competing risks of death for surgery and nonsurgical management. *Eur Urol*, 2014. 65: 235.
<https://www.ncbi.nlm.nih.gov/pubmed/23567066>
200. Sun, M., *et al.* Comparison of partial vs radical nephrectomy with regard to other-cause mortality in T1 renal cell carcinoma among patients aged ≥ 75 years with multiple comorbidities. *BJU Int*, 2013. 111: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/22612472>
201. Shuch, B., *et al.* Overall survival advantage with partial nephrectomy: a bias of observational data? *Cancer*, 2013. 119: 2981.
<https://www.ncbi.nlm.nih.gov/pubmed/23674264>
202. Weight, C.J., *et al.* Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. *J Urol*, 2010. 183: 1317.
<https://www.ncbi.nlm.nih.gov/pubmed/20171688>
203. Scosyrev, E., *et al.* Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. *Eur Urol*, 2014. 65: 372.
<https://www.ncbi.nlm.nih.gov/pubmed/23850254>
204. Antonelli, A., *et al.* Elective partial nephrectomy is equivalent to radical nephrectomy in patients with clinical T1 renal cell carcinoma: results of a retrospective, comparative, multi-institutional study. *BJU Int*, 2012. 109: 1013.
<https://www.ncbi.nlm.nih.gov/pubmed/21883829>
205. Badalato, G.M., *et al.* Survival after partial and radical nephrectomy for the treatment of stage T1bN0M0 renal cell carcinoma (RCC) in the USA: a propensity scoring approach. *BJU Int*, 2012. 109: 1457.
<https://www.ncbi.nlm.nih.gov/pubmed/21933334>
206. Poulakis, V., *et al.* Quality of life after surgery for localized renal cell carcinoma: comparison between radical nephrectomy and nephron-sparing surgery. *Urology*, 2003. 62: 814.
<https://www.ncbi.nlm.nih.gov/pubmed/14624900>
207. Shekarriz, B., *et al.* Comparison of costs and complications of radical and partial nephrectomy for treatment of localized renal cell carcinoma. *Urology*, 2002. 59: 211.
<https://www.ncbi.nlm.nih.gov/pubmed/11834387>
208. Van Poppel, H., *et al.* A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol*, 2007. 51: 1606.
<https://www.ncbi.nlm.nih.gov/pubmed/17140723>
209. Gabr, A.H., *et al.* Approach and specimen handling do not influence oncological perioperative and long-term outcomes after laparoscopic radical nephrectomy. *J Urol*, 2009. 182: 874.
<https://www.ncbi.nlm.nih.gov/pubmed/19616234>
210. Imamura M, *et al.* Systematic review of the clinical effectiveness of surgical management for localised renal cell carcinoma. University of Aberdeen, Academic Urology Unit, 2011.
[http://www.europeanurology.com/article/S0302-2838\(12\)00233-3](http://www.europeanurology.com/article/S0302-2838(12)00233-3)
211. Lane, B.R., *et al.* Management of the adrenal gland during partial nephrectomy. *J Urol*, 2009. 181: 2430.
<https://www.ncbi.nlm.nih.gov/pubmed/19371896>
212. Bekema, H.J., *et al.* Systematic review of adrenalectomy and lymph node dissection in locally advanced renal cell carcinoma. *Eur Urol*, 2013. 64: 799.
<https://www.ncbi.nlm.nih.gov/pubmed/23643550>
213. Blom, J.H., *et al.* Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. *Eur Urol*, 2009. 55: 28.
<https://www.ncbi.nlm.nih.gov/pubmed/18848382>
214. Capitanio, U., *et al.* Lymph node dissection in renal cell carcinoma. *Eur Urol*, 2011. 60: 1212.
<https://www.ncbi.nlm.nih.gov/pubmed/21940096>

215. Herrlinger, A., *et al.* What are the benefits of extended dissection of the regional renal lymph nodes in the therapy of renal cell carcinoma. *J Urol*, 1991. 146: 1224.
<https://www.ncbi.nlm.nih.gov/pubmed/1942267>
216. Peters, P.C., *et al.* The role of lymphadenectomy in the management of renal cell carcinoma. *Urol Clin North Am*, 1980. 7: 705.
<https://www.ncbi.nlm.nih.gov/pubmed/7456182>
217. Yamashita, Y. *et al.* The therapeutic value of lymph node dissection for renal cell carcinoma. *Nishinon J Urol*, 1989: 777. [No abstract available].
218. Sullivan, L.D., *et al.* Surgical management of renal cell carcinoma at the Vancouver General Hospital: 20-year review. *Can J Surg*, 1979. 22: 427.
<https://www.ncbi.nlm.nih.gov/pubmed/497910>
219. Siminovitch, J.P., *et al.* Lymphadenectomy in renal adenocarcinoma. *J Urol*, 1982. 127: 1090.
<https://www.ncbi.nlm.nih.gov/pubmed/7087013>
220. Kim S, *et al.* The relationship of lymph node dissection with recurrence and survival for patients treated with nephrectomy for high-risk renal cell carcinoma. *J Urol*, 2012. 187: e233.
[http://www.jurology.com/article/S0022-5347\(12\)01011-7/abstract](http://www.jurology.com/article/S0022-5347(12)01011-7/abstract)
221. Dimashkieh, H.H., *et al.* Extranodal extension in regional lymph nodes is associated with outcome in patients with renal cell carcinoma. *J Urol*, 2006. 176: 1978.
<https://www.ncbi.nlm.nih.gov/pubmed/17070225>
222. Terrone, C., *et al.* Reassessing the current TNM lymph node staging for renal cell carcinoma. *Eur Urol*, 2006. 49: 324.
<https://www.ncbi.nlm.nih.gov/pubmed/16386352>
223. Whitson, J.M., *et al.* Population-based comparative effectiveness of nephron-sparing surgery vs ablation for small renal masses. *BJU Int*, 2012. 110: 1438.
<https://www.ncbi.nlm.nih.gov/pubmed/22639860>
224. Capitano, U., *et al.* Extent of lymph node dissection at nephrectomy affects cancer-specific survival and metastatic progression in specific sub-categories of patients with renal cell carcinoma (RCC). *BJU Int*, 2014. 114: 210.
<https://www.ncbi.nlm.nih.gov/pubmed/24854206>
225. Chapin, B.F., *et al.* The role of lymph node dissection in renal cell carcinoma. *Int J Clin Oncol*, 2011. 16: 186.
<https://www.ncbi.nlm.nih.gov/pubmed/21523561>
226. Kwon, T., *et al.* Reassessment of renal cell carcinoma lymph node staging: analysis of patterns of progression. *Urology*, 2011. 77: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/20817274>
227. Bex, A., *et al.* Intraoperative sentinel node identification and sampling in clinically node-negative renal cell carcinoma: initial experience in 20 patients. *World J Urol*, 2011. 29: 793.
<https://www.ncbi.nlm.nih.gov/pubmed/21107845>
228. Sherif, A.M., *et al.* Sentinel node detection in renal cell carcinoma. A feasibility study for detection of tumour-draining lymph nodes. *BJU Int*, 2012. 109: 1134.
<https://www.ncbi.nlm.nih.gov/pubmed/21883833>
229. May, M., *et al.* Pre-operative renal arterial embolisation does not provide survival benefit in patients with radical nephrectomy for renal cell carcinoma. *Br J Radiol*, 2009. 82: 724.
<https://www.ncbi.nlm.nih.gov/pubmed/19255117>
230. Subramanian, V.S., *et al.* Utility of preoperative renal artery embolization for management of renal tumors with inferior vena caval thrombi. *Urology*, 2009. 74: 154.
<https://www.ncbi.nlm.nih.gov/pubmed/19428069>
231. Maxwell, N.J., *et al.* Renal artery embolisation in the palliative treatment of renal carcinoma. *Br J Radiol*, 2007. 80: 96.
<https://www.ncbi.nlm.nih.gov/pubmed/17495058>
232. Hallscheidt, P., *et al.* [Preoperative and palliative embolization of renal cell carcinomas: follow-up of 49 patients]. *Rofo*, 2006. 178: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/16612730>
233. Lamb, G.W., *et al.* Management of renal masses in patients medically unsuitable for nephrectomy--natural history, complications, and outcome. *Urology*, 2004. 64: 909.
<https://www.ncbi.nlm.nih.gov/pubmed/15533476>
234. Hemal, A.K., *et al.* Laparoscopic versus open radical nephrectomy for large renal tumors: a long-term prospective comparison. *J Urol*, 2007. 177: 862.
<https://www.ncbi.nlm.nih.gov/pubmed/17296361>

235. Brewer, K., *et al.* Perioperative and renal function outcomes of minimally invasive partial nephrectomy for T1b and T2a kidney tumors. *J Endourol*, 2012. 26: 244.
<https://www.ncbi.nlm.nih.gov/pubmed/22192099>
236. Sprenkle, P.C., *et al.* Comparison of open and minimally invasive partial nephrectomy for renal tumors 4-7 centimeters. *Eur Urol*, 2012. 61: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/22154728>
237. Peng B, *et al.* Retroperitoneal laparoscopic nephrectomy and open nephrectomy for radical treatment of renal cell carcinoma: A comparison of clinical outcomes. *Acad J Sec Milit Med Univ*, 2006: 1167.
<https://www.researchgate.net/publication/283136329>
238. Ebbing, J., *et al.* Evaluation of perioperative complications in open and laparoscopic surgery for renal cell cancer with tumor thrombus involvement using the Clavien-Dindo classification. *Eur J Surg Oncol*, 2015. 41: 941.
<https://www.ncbi.nlm.nih.gov/pubmed/25817982>
239. Laird, A., *et al.* Matched pair analysis of laparoscopic versus open radical nephrectomy for the treatment of T3 renal cell carcinoma. *World J Urol*, 2015. 33: 25.
<https://www.ncbi.nlm.nih.gov/pubmed/24647880>
240. Steinberg, A.P., *et al.* Laparoscopic radical nephrectomy for large (greater than 7 cm, T2) renal tumors. *J Urol*, 2004. 172: 2172.
<https://www.ncbi.nlm.nih.gov/pubmed/15538225>
241. Jeon, S.H., *et al.* Comparison of laparoscopic versus open radical nephrectomy for large renal tumors: a retrospective analysis of multi-center results. *BJU Int*, 2011. 107: 817.
<https://www.ncbi.nlm.nih.gov/pubmed/21029315>
242. Hattori, R., *et al.* Laparoscopic radical nephrectomy for large renal-cell carcinomas. *J Endourol*, 2009. 23: 1523.
<https://www.ncbi.nlm.nih.gov/pubmed/19698022>
243. Desai, M.M., *et al.* Prospective randomized comparison of transperitoneal versus retroperitoneal laparoscopic radical nephrectomy. *J Urol*, 2005. 173: 38.
<https://www.ncbi.nlm.nih.gov/pubmed/15592021>
244. Nambirajan, T., *et al.* Prospective, randomized controlled study: transperitoneal laparoscopic versus retroperitoneoscopic radical nephrectomy. *Urology*, 2004. 64: 919.
<https://www.ncbi.nlm.nih.gov/pubmed/15533478>
245. Nadler, R.B., *et al.* A prospective study of laparoscopic radical nephrectomy for T1 tumors--is transperitoneal, retroperitoneal or hand assisted the best approach? *J Urol*, 2006. 175: 1230.
<https://www.ncbi.nlm.nih.gov/pubmed/16515966>
246. Hemal, A.K., *et al.* A prospective comparison of laparoscopic and robotic radical nephrectomy for T1-2N0M0 renal cell carcinoma. *World J Urol*, 2009. 27: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/18704439>
247. Soga, N., *et al.* Comparison of radical nephrectomy techniques in one center: minimal incision portless endoscopic surgery versus laparoscopic surgery. *Int J Urol*, 2008. 15: 1018.
<https://www.ncbi.nlm.nih.gov/pubmed/19138194>
248. Park Y, *et al.* Laparoendoscopic single-site radical nephrectomy for localized renal cell carcinoma: comparison with conventional laparoscopic surgery. *J Endourol* 2009. 23: A19. [No abstract available].
249. Gill, I.S., *et al.* Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. *J Urol*, 2007. 178: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/17574056>
250. Lane, B.R., *et al.* 7-year oncological outcomes after laparoscopic and open partial nephrectomy. *J Urol*, 2010. 183: 473.
<https://www.ncbi.nlm.nih.gov/pubmed/20006866>
251. Gong, E.M., *et al.* Comparison of laparoscopic and open partial nephrectomy in clinical T1a renal tumors. *J Endourol*, 2008. 22: 953.
<https://www.ncbi.nlm.nih.gov/pubmed/18363510>
252. Marszalek, M., *et al.* Laparoscopic and open partial nephrectomy: a matched-pair comparison of 200 patients. *Eur Urol*, 2009. 55: 1171.
<https://www.ncbi.nlm.nih.gov/pubmed/19232819>
253. Kaneko, G., *et al.* The benefit of laparoscopic partial nephrectomy in high body mass index patients. *Jpn J Clin Oncol*, 2012. 42: 619.
<https://www.ncbi.nlm.nih.gov/pubmed/22561514>

254. Muramaki, M., *et al.* Prognostic Factors Influencing Postoperative Development of Chronic Kidney Disease in Patients with Small Renal Tumors who Underwent Partial Nephrectomy. *Curr Urol*, 2013. 6: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/24917730>
255. Tugcu, V., *et al.* Transperitoneal versus retroperitoneal laparoscopic partial nephrectomy: initial experience. *Arch Ital Urol Androl*, 2011. 83: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/22670314>
256. Minervini, A., *et al.* Simple enucleation versus radical nephrectomy in the treatment of pT1a and pT1b renal cell carcinoma. *Ann Surg Oncol*, 2012. 19: 694.
<https://www.ncbi.nlm.nih.gov/pubmed/21861225>
257. Minervini, A., *et al.* Simple enucleation is equivalent to traditional partial nephrectomy for renal cell carcinoma: results of a nonrandomized, retrospective, comparative study. *J Urol*, 2011. 185: 1604.
<https://www.ncbi.nlm.nih.gov/pubmed/21419454>
258. Nisen, H., *et al.* Hand-assisted laparoscopic versus open partial nephrectomy in patients with T1 renal tumor: Comparative perioperative, functional and oncological outcome. *Scand J Urol*, 2015: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/26317448>
259. Rais-Bahrami, S., *et al.* Off-clamp versus complete hilar control laparoscopic partial nephrectomy: comparison by clinical stage. *BJU Int*, 2012. 109: 1376.
<https://www.ncbi.nlm.nih.gov/pubmed/21992566>
260. Bazzi, W.M., *et al.* Comparison of laparoendoscopic single-site and multiport laparoscopic radical and partial nephrectomy: a prospective, nonrandomized study. *Urology*, 2012. 80: 1039.
<https://www.ncbi.nlm.nih.gov/pubmed/22990064>
261. Masson-Lecomte, A., *et al.* A prospective comparison of the pathologic and surgical outcomes obtained after elective treatment of renal cell carcinoma by open or robot-assisted partial nephrectomy. *Urol Oncol*, 2013. 31: 924.
<https://www.ncbi.nlm.nih.gov/pubmed/21906969>
262. Choi, J.E., *et al.* Comparison of perioperative outcomes between robotic and laparoscopic partial nephrectomy: a systematic review and meta-analysis. *Eur Urol*, 2015. 67: 891.
<https://www.ncbi.nlm.nih.gov/pubmed/25572825>
263. Shah, P.H., *et al.* Positive Surgical Margins Increase Risk of Recurrence after Partial Nephrectomy for High Risk Renal Tumors. *J Urol*, 2016. 196: 327.
<https://www.ncbi.nlm.nih.gov/pubmed/26907508>
264. Tabayoyong, W., *et al.* Variation in Surgical Margin Status by Surgical Approach among Patients Undergoing Partial Nephrectomy for Small Renal Masses. *J Urol*, 2015. 194: 1548.
<https://www.ncbi.nlm.nih.gov/pubmed/26094808>
265. Porpiglia, F., *et al.* Partial Nephrectomy in Clinical T1b Renal Tumors: Multicenter Comparative Study of Open, Laparoscopic and Robot-assisted Approach (the RECORd Project). *Urology*, 2016. 89: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/26743388>
266. Steinestel, J., *et al.* Positive surgical margins in nephron-sparing surgery: risk factors and therapeutic consequences. *World J Surg Oncol*, 2014. 12: 252.
<https://www.ncbi.nlm.nih.gov/pubmed/25103683>
267. Bensalah, K., *et al.* Positive surgical margin appears to have negligible impact on survival of renal cell carcinomas treated by nephron-sparing surgery. *Eur Urol*, 2010. 57: 466.
<https://www.ncbi.nlm.nih.gov/pubmed/19359089>
268. Lopez-Costea, M.A., *et al.* Oncological outcomes and prognostic factors after nephron-sparing surgery in renal cell carcinoma. *Int Urol Nephrol*, 2016. 48: 681.
<https://www.ncbi.nlm.nih.gov/pubmed/26861062>
269. Sundaram, V., *et al.* Positive margin during partial nephrectomy: does cancer remain in the renal remnant? *Urology*, 2011. 77: 1400.
<https://www.ncbi.nlm.nih.gov/pubmed/21411126>
270. Kim, S.P., *et al.* Treatment of Patients with Positive Margins after Partial Nephrectomy. *J Urol*, 2016. 196: 301.
<https://www.ncbi.nlm.nih.gov/pubmed/27188474>
271. Antic, T., *et al.* Partial nephrectomy for renal tumors: lack of correlation between margin status and local recurrence. *Am J Clin Pathol*, 2015. 143: 645.
<https://www.ncbi.nlm.nih.gov/pubmed/25873497>
272. Zini, L., *et al.* A population-based comparison of survival after nephrectomy vs nonsurgical management for small renal masses. *BJU Int*, 2009. 103: 899.
<https://www.ncbi.nlm.nih.gov/pubmed/19154499>

273. Sun, M., *et al.* 1634 Management of localized kidney cancer: calculating cancer-specific mortality and competing-risks of death tradeoffs between surgery and active surveillance. *J Urol*, 2013. 189: e672.
<http://www.sciencedirect.com/science/article/pii/S0022534713033764>
274. Huang WC, *et al.* Surveillance for the management of small renal masses: outcomes in a population-based cohort. *J Urol*, 2013: e483.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2748741/>
275. Hyams ES, *et al.* Partial nephrectomy vs. Non-surgical management for small renal masses: a population-based comparison of disease-specific and overall survival. *J Urol*, 2012. 187: E678.
[http://www.jurology.com/article/S0022-5347\(12\)01914-3/abstract](http://www.jurology.com/article/S0022-5347(12)01914-3/abstract)
276. Lane, B.R., *et al.* Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. *Cancer*, 2010. 116: 3119.
<https://www.ncbi.nlm.nih.gov/pubmed/20564627>
277. Hollingsworth, J.M., *et al.* Five-year survival after surgical treatment for kidney cancer: a population-based competing risk analysis. *Cancer*, 2007. 109: 1763.
<https://www.ncbi.nlm.nih.gov/pubmed/17351954>
278. Volpe, A., *et al.* The natural history of incidentally detected small renal masses. *Cancer*, 2004. 100: 738.
<https://www.ncbi.nlm.nih.gov/pubmed/14770429>
279. Jewett, M.A., *et al.* Active surveillance of small renal masses: progression patterns of early stage kidney cancer. *Eur Urol*, 2011. 60: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/21477920>
280. Smaldone, M.C., *et al.* Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. *Cancer*, 2012. 118: 997.
<https://www.ncbi.nlm.nih.gov/pubmed/21766302>
281. Patel, N., *et al.* Active surveillance of small renal masses offers short-term oncological efficacy equivalent to radical and partial nephrectomy. *BJU Int*, 2012. 110: 1270.
<https://www.ncbi.nlm.nih.gov/pubmed/22564495>
282. Pierorazio, P.M., *et al.* Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. *Eur Urol*, 2015. 68: 408.
<https://www.ncbi.nlm.nih.gov/pubmed/25698065>
283. Abou Youssif, T., *et al.* Active surveillance for selected patients with renal masses: updated results with long-term follow-up. *Cancer*, 2007. 110: 1010.
<https://www.ncbi.nlm.nih.gov/pubmed/17628489>
284. Abouassaly, R., *et al.* Active surveillance of renal masses in elderly patients. *J Urol*, 2008. 180: 505.
<https://www.ncbi.nlm.nih.gov/pubmed/18550113>
285. Crispen, P.L., *et al.* Natural history, growth kinetics, and outcomes of untreated clinically localized renal tumors under active surveillance. *Cancer*, 2009. 115: 2844.
<https://www.ncbi.nlm.nih.gov/pubmed/19402168>
286. Rosales, J.C., *et al.* Active surveillance for renal cortical neoplasms. *J Urol*, 2010. 183: 1698.
<https://www.ncbi.nlm.nih.gov/pubmed/20299038>
287. Pierorazio P, *et al.* Quality of life on active surveillance for small masses versus immediate intervention: interim analysis of the DISSRM (delayed intervention and surveillance for small renal masses) registry. *J Urol*, 2013. 189: e259. [No abstract available].
288. Sisul, D.M., *et al.* RENAL nephrometry score is associated with complications after renal cryoablation: a multicenter analysis. *Urology*, 2013. 81: 775.
<https://www.ncbi.nlm.nih.gov/pubmed/23434099>
289. Kim EH, *et al.* Outcomes of laparoscopic and percutaneous cryoablation for renal masses. *J Urol*, 2013. 189: e492. [No abstract available].
290. Goyal, J., *et al.* Single-center comparative oncologic outcomes of surgical and percutaneous cryoablation for treatment of renal tumors. *J Endourol*, 2012. 26: 1413.
<https://www.ncbi.nlm.nih.gov/pubmed/22642574>
291. Zargar, H., *et al.* Cryoablation for Small Renal Masses: Selection Criteria, Complications, and Functional and Oncologic Results. *Eur Urol*, 2016. 69: 116.
<https://www.ncbi.nlm.nih.gov/pubmed/25819723>
292. O'Malley, R.L., *et al.* A matched-cohort comparison of laparoscopic cryoablation and laparoscopic partial nephrectomy for treating renal masses. *BJU Int*, 2007. 99: 395.
<https://www.ncbi.nlm.nih.gov/pubmed/17092288>

293. Ko, Y.H., *et al.* A matched-cohort comparison of laparoscopic renal cryoablation using ultra-thin cryoprobes with open partial nephrectomy for the treatment of small renal cell carcinoma. *Cancer Res Treat*, 2008. 40: 184.
<https://www.ncbi.nlm.nih.gov/pubmed/19688128>
294. Desai, M.M., *et al.* Laparoscopic partial nephrectomy versus laparoscopic cryoablation for the small renal tumor. *Urology*, 2005. 66: 23.
<https://www.ncbi.nlm.nih.gov/pubmed/16194703>
295. Haber, G.P., *et al.* Tumour in solitary kidney: laparoscopic partial nephrectomy vs laparoscopic cryoablation. *BJU Int*, 2012. 109: 118.
<https://www.ncbi.nlm.nih.gov/pubmed/21895929>
296. Guillotreau, J., *et al.* Robotic partial nephrectomy versus laparoscopic cryoablation for the small renal mass. *Eur Urol*, 2012. 61: 899.
<https://www.ncbi.nlm.nih.gov/pubmed/22264680>
297. Klatte, T., *et al.* Perioperative, oncologic, and functional outcomes of laparoscopic renal cryoablation and open partial nephrectomy: a matched pair analysis. *J Endourol*, 2011. 25: 991.
<https://www.ncbi.nlm.nih.gov/pubmed/21568698>
298. Lian, H., *et al.* Single-center comparison of complications in laparoscopic and percutaneous radiofrequency ablation with ultrasound guidance for renal tumors. *Urology*, 2012. 80: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/22633890>
299. Young, E.E., *et al.* Comparison of safety, renal function outcomes and efficacy of laparoscopic and percutaneous radio frequency ablation of renal masses. *J Urol*, 2012. 187: 1177.
<https://www.ncbi.nlm.nih.gov/pubmed/22357170>
300. Kim, S.D., *et al.* Radiofrequency ablation of renal tumors: four-year follow-up results in 47 patients. *Korean J Radiol*, 2012. 13: 625.
<https://www.ncbi.nlm.nih.gov/pubmed/22977331>
301. Trudeau, V., *et al.* Comparison of Postoperative Complications and Mortality Between Laparoscopic and Percutaneous Local Tumor Ablation for T1a Renal Cell Carcinoma: A Population-based Study. *Urology*, 2016. 89: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/26514977>
302. Takaki, H., *et al.* Midterm results of radiofrequency ablation versus nephrectomy for T1a renal cell carcinoma. *Jpn J Radiol*, 2010. 28: 460.
<https://www.ncbi.nlm.nih.gov/pubmed/20661697>
303. Olweny, E.O., *et al.* Radiofrequency ablation versus partial nephrectomy in patients with solitary clinical T1a renal cell carcinoma: comparable oncologic outcomes at a minimum of 5 years of follow-up. *Eur Urol*, 2012. 61: 1156.
<https://www.ncbi.nlm.nih.gov/pubmed/22257424>
304. Arnoux, V., *et al.* [Perioperative outcomes and mid-term results of radiofrequency ablation and partial nephrectomy in indications of renal tumor treatment and imperative nephron-sparing procedure]. *Prog Urol*, 2013. 23: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/23352302>
305. Pan, X.W., *et al.* Radiofrequency ablation versus partial nephrectomy for treatment of renal masses: A systematic review and meta-analysis. *Kaohsiung J Med Sci*, 2015. 31: 649.
<https://www.ncbi.nlm.nih.gov/pubmed/26709228>
306. Atwell, T.D., *et al.* Percutaneous ablation of renal masses measuring 3.0 cm and smaller: comparative local control and complications after radiofrequency ablation and cryoablation. *AJR Am J Roentgenol*, 2013. 200: 461.
<https://www.ncbi.nlm.nih.gov/pubmed/23345372>
307. Samarasekera D, *et al.* Percutaneous radiofrequency ablation versus percutaneous cryoablation: long-term outcomes following ablation for renal cell carcinoma. *J Urol*, 2013. 189: e737.
[http://www.jurology.com/article/S0022-5347\(13\)03121-2/abstract](http://www.jurology.com/article/S0022-5347(13)03121-2/abstract)
308. Nesbitt, J.C., *et al.* Surgical management of renal cell carcinoma with inferior vena cava tumor thrombus. *Ann Thorac Surg*, 1997. 63: 1592.
<https://www.ncbi.nlm.nih.gov/pubmed/9205155>
309. Hatcher, P.A., *et al.* Surgical management and prognosis of renal cell carcinoma invading the vena cava. *J Urol*, 1991. 145: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/1984092>
310. Neves, R.J., *et al.* Surgical treatment of renal cancer with vena cava extension. *Br J Urol*, 1987. 59: 390.
<https://www.ncbi.nlm.nih.gov/pubmed/3594097>

311. Haferkamp, A., *et al.* Renal cell carcinoma with tumor thrombus extension into the vena cava: prospective long-term followup. *J Urol*, 2007. 177: 1703.
<https://www.ncbi.nlm.nih.gov/pubmed/17437789>
312. Kirkali, Z., *et al.* A critical analysis of surgery for kidney cancer with vena cava invasion. *Eur Urol*, 2007. 52: 658.
<https://www.ncbi.nlm.nih.gov/pubmed/17548146>
313. Moinzadeh, A., *et al.* Prognostic significance of tumor thrombus level in patients with renal cell carcinoma and venous tumor thrombus extension. Is all T3b the same? *J Urol*, 2004. 171: 598.
<https://www.ncbi.nlm.nih.gov/pubmed/14713768>
314. Kaplan, S., *et al.* Surgical management of renal cell carcinoma with inferior vena cava tumor thrombus. *Am J Surg*, 2002. 183: 292.
<https://www.ncbi.nlm.nih.gov/pubmed/11943130>
315. Bissada, N.K., *et al.* Long-term experience with management of renal cell carcinoma involving the inferior vena cava. *Urology*, 2003. 61: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/12559273>
316. Skinner, D.G., *et al.* Vena caval involvement by renal cell carcinoma. Surgical resection provides meaningful long-term survival. *Ann Surg*, 1989. 210: 387.
<https://www.ncbi.nlm.nih.gov/pubmed/2774709>
317. Lardas, M., *et al.* Systematic Review of Surgical Management of Nonmetastatic Renal Cell Carcinoma with Vena Caval Thrombus. *Eur Urol*, 2016.70: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/26707869>
318. Ljungberg B., *et al.* Systematic Review Methodology for the European Association of Urology Guidelines for Renal Cell Carcinoma (2014 update).
https://uroweb.org/wp-content/uploads/Systematic_methodology_RCC_2014_update.pdf
319. Wotkowicz, C., *et al.* Management of renal cell carcinoma with vena cava and atrial thrombus: minimal access vs median sternotomy with circulatory arrest. *BJU Int*, 2006. 98: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/16879667>
320. Faust W, *et al.* Minimal access versus median sternotomy for cardiopulmonary bypass in the management of renal cell carcinoma with vena caval and atrial involvement. *J Urol*, 2013. 189 (Suppl.): e255. [No abstract available].
321. Chan AA, *et al.* Impact of preoperative renal artery embolization on surgical outcomes and overall survival in patients with renal cell carcinoma and inferior vena cava thrombus. *J Urol*, 2011: e707. [No abstract available].
322. Orihashi, K., *et al.* Deep hypothermic circulatory arrest for resection of renal tumor in the inferior vena cava: beneficial or deleterious? *Circ J*, 2008. 72: 1175.
<https://www.ncbi.nlm.nih.gov/pubmed/18577831>
323. Galligioni, E., *et al.* Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guerin: five-year results of a prospective randomized study. *Cancer*, 1996. 77: 2560.
<https://www.ncbi.nlm.nih.gov/pubmed/8640706>
324. Figlin, R.A., *et al.* Multicenter, randomized, phase III trial of CD8(+) tumor-infiltrating lymphocytes in combination with recombinant interleukin-2 in metastatic renal cell carcinoma. *J Clin Oncol*, 1999. 17: 2521.
<https://www.ncbi.nlm.nih.gov/pubmed/10561318>
325. Clark, J.I., *et al.* Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. *J Clin Oncol*, 2003. 21: 3133.
<https://www.ncbi.nlm.nih.gov/pubmed/12810695>
326. Atzpodiën, J., *et al.* Adjuvant treatment with interleukin-2- and interferon-alpha2a-based chemoimmunotherapy in renal cell carcinoma post tumour nephrectomy: results of a prospectively randomised trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN). *Br J Cancer*, 2005. 92: 843.
<https://www.ncbi.nlm.nih.gov/pubmed/15756254>
327. Jocham, D., *et al.* Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. *Lancet*, 2004. 363: 594.
<https://www.ncbi.nlm.nih.gov/pubmed/14987883>
328. Janowitz, T., *et al.* Adjuvant therapy in renal cell carcinoma-past, present, and future. *Semin Oncol*, 2013. 40: 482.
<https://www.ncbi.nlm.nih.gov/pubmed/23972712>

329. Wood, C., *et al.* An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. *Lancet*, 2008. 372: 145.
<https://www.ncbi.nlm.nih.gov/pubmed/18602688>
330. Chamie, K., *et al.* Carbonic anhydrase-IX score is a novel biomarker that predicts recurrence and survival for high-risk, nonmetastatic renal cell carcinoma: Data from the phase III ARISER clinical trial. *Urol Oncol*, 2015. 33: 204 e25.
<https://www.ncbi.nlm.nih.gov/pubmed/25823535>
331. Ravaud, A., *et al.* Phase III trial of sunitinib (SU) vs placebo (PBO) as adjuvant treatment for high-risk renal cell carcinoma (RCC) after nephrectomy (S-TRAC). *Ann Oncol* 2016. 27: LBA1.
<https://academic.oup.com/annonc/article-abstract/doi/10.1093/annonc/mdw435.22/2800531/genitourinary-tumours-non-prostatePhase-III-trial>
332. Flanigan, R.C., *et al.* Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol*, 2004. 171: 1071.
<https://www.ncbi.nlm.nih.gov/pubmed/14767273>
333. Dabestani, S., *et al.* Local treatments for metastases of renal cell carcinoma: a systematic review. *Lancet Oncol*, 2014. 15: e549.
<https://www.ncbi.nlm.nih.gov/pubmed/25439697>
334. Dabestani S, *et al.* EAU Renal Cell Carcinoma Guideline Panel. Systematic review methodology for the EAU RCC Guideline 2013 update. 2013.
https://uroweb.org/wp-content/uploads/Systematic_methodology_RCC_2014_update.pdf
335. Alt, A.L., *et al.* Survival after complete surgical resection of multiple metastases from renal cell carcinoma. *Cancer*, 2011. 117: 2873.
<https://www.ncbi.nlm.nih.gov/pubmed/21692048>
336. Brinkmann OA, *et al.* The role of residual tumor resection in patients with metastatic renal cell carcinoma and partial remission following immunotherapy. *Eur Urol*, 2007: 641.
<https://www.researchgate.net/publication/271563765>
337. Kwak, C., *et al.* Metastasectomy without systemic therapy in metastatic renal cell carcinoma: comparison with conservative treatment. *Urol Int*, 2007. 79: 145.
<https://www.ncbi.nlm.nih.gov/pubmed/17851285>
338. Lee, S.E., *et al.* Metastasectomy prior to immunochemotherapy for metastatic renal cell carcinoma. *Urol Int*, 2006. 76: 256.
<https://www.ncbi.nlm.nih.gov/pubmed/16601390>
339. Petralia G, *et al.* Complete metastasectomy is an independent predictor of cancer-specific survival in patients with clinically metastatic renal cell carcinoma. *Eur Urol Suppl* 2010, 2010: 162.
[http://www.europeanurology.com/article/S1569-9056\(10\)60446-0/abstract/450](http://www.europeanurology.com/article/S1569-9056(10)60446-0/abstract/450)
340. Russo, P., *et al.* Cytoreductive nephrectomy and nephrectomy/complete metastasectomy for metastatic renal cancer. *ScientificWorldJournal*, 2007. 7: 768.
<https://www.ncbi.nlm.nih.gov/pubmed/17619759>
341. Staehler M, *et al.* Metastasectomy significantly prolongs survival in patients with metastatic renal cancer. *Eur Urol Suppl* 2009, 2009: 181. [No abstract available].
342. Eggener, S.E., *et al.* Risk score and metastasectomy independently impact prognosis of patients with recurrent renal cell carcinoma. *J Urol*, 2008. 180: 873.
<https://www.ncbi.nlm.nih.gov/pubmed/18635225>
343. Fuchs, B., *et al.* Solitary bony metastasis from renal cell carcinoma: significance of surgical treatment. *Clin Orthop Relat Res*, 2005: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/15685074>
344. Hunter, G.K., *et al.* The efficacy of external beam radiotherapy and stereotactic body radiotherapy for painful spinal metastases from renal cell carcinoma. *Pract Radiat Oncol*, 2012. 2: e95.
<https://www.ncbi.nlm.nih.gov/pubmed/24674192>
345. Zelefsky, M.J., *et al.* Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys*, 2012. 82: 1744.
<https://www.ncbi.nlm.nih.gov/pubmed/21596489>
346. Fokas, E., *et al.* Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients. *Strahlenther Onkol*, 2010. 186: 210.
<https://www.ncbi.nlm.nih.gov/pubmed/20165820>

347. Ikushima, H., *et al.* Fractionated stereotactic radiotherapy of brain metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys*, 2000. 48: 1389.
<https://www.ncbi.nlm.nih.gov/pubmed/11121638>
348. Staehler, M.D., *et al.* Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis. *World J Urol*, 2010. 28: 543.
<https://www.ncbi.nlm.nih.gov/pubmed/20440505>
349. Amiraliev A, *et al.* Treatment strategy in patients with pulmonary metastases of renal cell cancer. *Int Cardio Thor Surg*, 2012: S20.
<https://www.ncbi.nlm.nih.gov/pubmed/>
350. Zerbi, A., *et al.* Pancreatic metastasis from renal cell carcinoma: which patients benefit from surgical resection? *Ann Surg Oncol*, 2008. 15: 1161.
<https://www.ncbi.nlm.nih.gov/pubmed/18196343>
351. Kickuth, R., *et al.* Interventional management of hypervascular osseous metastasis: role of embolotherapy before orthopedic tumor resection and bone stabilization. *AJR Am J Roentgenol*, 2008. 191: W240.
<https://www.ncbi.nlm.nih.gov/pubmed/19020210>
352. Forauer, A.R., *et al.* Selective palliative transcatheter embolization of bony metastases from renal cell carcinoma. *Acta Oncol*, 2007. 46: 1012.
<https://www.ncbi.nlm.nih.gov/pubmed/17851849>
353. Stadler, W.M., *et al.* Prognostic factors for survival with gemcitabine plus 5-fluorouracil based regimens for metastatic renal cancer. *J Urol*, 2003. 170: 1141.
<https://www.ncbi.nlm.nih.gov/pubmed/14501711>
354. Gore, M.E., *et al.* Interferon alfa-2a versus combination therapy with interferon alfa-2a, interleukin-2, and fluorouracil in patients with untreated metastatic renal cell carcinoma (MRC RE04/EORTC GU 30012): an open-label randomised trial. *Lancet*, 2010. 375: 641.
<https://www.ncbi.nlm.nih.gov/pubmed/20153039>
355. Haas, N.B., *et al.* A phase II trial of doxorubicin and gemcitabine in renal cell carcinoma with sarcomatoid features: ECOG 8802. *Med Oncol*, 2012. 29: 761.
<https://www.ncbi.nlm.nih.gov/pubmed/21298497>
356. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Medical Research Council Renal Cancer Collaborators. *Lancet*, 1999. 353: 14.
<https://www.ncbi.nlm.nih.gov/pubmed/10023944>
357. Motzer, R.J., *et al.* Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol*, 2002. 20: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/11773181>
358. Coppin, C., *et al.* Immunotherapy for advanced renal cell cancer. *Cochrane Database Syst Rev*, 2005: CD001425.
<https://www.ncbi.nlm.nih.gov/pubmed/15674877>
359. Negrier, S., *et al.* Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer*, 2007. 110: 2468.
<https://www.ncbi.nlm.nih.gov/pubmed/17932908>
360. Escudier, B., *et al.* Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*, 2007. 370: 2103.
<https://www.ncbi.nlm.nih.gov/pubmed/18156031>
361. Motzer, R.J., *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*, 2007. 356: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/17215529>
362. Hudes, G., *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*, 2007. 356: 2271.
<https://www.ncbi.nlm.nih.gov/pubmed/17538086>
363. Rosenberg, S.A., *et al.* Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. *J Natl Cancer Inst*, 1993. 85: 622.
<https://www.ncbi.nlm.nih.gov/pubmed/8468720>
364. Heng, D.Y., *et al.* Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*, 2009. 27: 5794.
<https://www.ncbi.nlm.nih.gov/pubmed/21741163>

365. Fyfe, G., *et al.* Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol*, 1995. 13: 688.
<https://www.ncbi.nlm.nih.gov/pubmed/7884429>
366. McDermott, D.F., *et al.* Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 2005. 23: 133.
<https://www.ncbi.nlm.nih.gov/pubmed/15625368>
367. Yang, J.C., *et al.* Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol*, 2003. 21: 3127.
<https://www.ncbi.nlm.nih.gov/pubmed/12915604>
368. Amato, R.J., *et al.* Vaccination of metastatic renal cancer patients with MVA-5T4: a randomized, double-blind, placebo-controlled phase III study. *Clin Cancer Res*, 2010. 16: 5539.
<https://www.ncbi.nlm.nih.gov/pubmed/20881001>
369. Brahmer, J.R., *et al.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*, 2012. 366: 2455.
<https://www.ncbi.nlm.nih.gov/pubmed/22658128>
370. Ribas, A. Tumor immunotherapy directed at PD-1. *N Engl J Med*, 2012. 366: 2517.
<https://www.ncbi.nlm.nih.gov/pubmed/22658126>
371. Motzer, R.J., *et al.* Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. *J Clin Oncol*, 2015. 33: 1430.
<https://www.ncbi.nlm.nih.gov/pubmed/25452452>
372. Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214). 2015.
<http://meetinglibrary.asco.org/content/145999-156>
373. Study of Nivolumab (BMS-936558) vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma (CheckMate 025). 2015. 2015.
<https://clinicaltrials.gov/ct2/show/NCT01668784>
374. Patel, P.H., *et al.* Targeting von Hippel-Lindau pathway in renal cell carcinoma. *Clin Cancer Res*, 2006. 12: 7215.
<https://www.ncbi.nlm.nih.gov/pubmed/https://clinicaltrials.gov/ct2/show/NCT01668784>
375. Yang, J.C., *et al.* A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med*, 2003. 349: 427.
<https://www.ncbi.nlm.nih.gov/pubmed/12890841>
376. Patard, J.J., *et al.* Understanding the importance of smart drugs in renal cell carcinoma. *Eur Urol*, 2006. 49: 633.
<https://www.ncbi.nlm.nih.gov/pubmed/16481093>
377. Harshman, L.C., *et al.* Conditional survival of patients with metastatic renal-cell carcinoma treated with VEGF-targeted therapy: a population-based study. *Lancet Oncol*, 2012. 13: 927.
<https://www.ncbi.nlm.nih.gov/pubmed/22877847>
378. Heng, D.Y., *et al.* External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*, 2013. 14: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/23312463>
379. Ko, J.J., *et al.* The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. *Lancet Oncol*, 2015. 16: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/25681967>
380. Escudier, B., *et al.* Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*, 2007. 356: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/17215530>
381. Bellmunt, J., *et al.* The medical treatment of metastatic renal cell cancer in the elderly: position paper of a SIOG Taskforce. *Crit Rev Oncol Hematol*, 2009. 69: 64.
<https://www.ncbi.nlm.nih.gov/pubmed/18774306>
382. Motzer, R.J., *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 2006. 24: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/16330672>
383. Motzer, R.J., *et al.* Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 2009. 27: 3584.
<https://www.ncbi.nlm.nih.gov/pubmed/19487381>

384. Motzer, R.J., *et al.* Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. *J Clin Oncol*, 2012. 30: 1371.
<https://www.ncbi.nlm.nih.gov/pubmed/22430274>
385. Bracarda, S., *et al.* Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. *Ann Oncol*, 2016. 27: 366.
<https://www.ncbi.nlm.nih.gov/pubmed/26685011>
386. Sternberg, C.N., *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*, 2010. 28: 1061.
<https://www.ncbi.nlm.nih.gov/pubmed/20100962>
387. Motzer, R.J., *et al.* Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*, 2013. 369: 722.
<https://www.ncbi.nlm.nih.gov/pubmed/23964934>
388. Escudier BJ. *et al.* Patient preference between pazopanib (Paz) and sunitinib (Sun): Results of a randomized double-blind, placebo-controlled, cross-over study in patients with metastatic renal cell carcinoma (mRCC)—PISCES study, NCT 01064310. *J Clin Oncol* 2012. 30.
<http://meetinglibrary.asco.org/content/98799-114>
389. Rini, B.I., *et al.* Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*, 2011. 378: 1931.
<https://www.ncbi.nlm.nih.gov/pubmed/22056247>
390. Dror Michaelson M., *et al.* Phase III AXIS trial of axitinib versus sorafenib in metastatic renal cell carcinoma: Updated results among cytokine-treated patients. *J Clin Oncol* 2012. *J Clin Oncol* 30, 2012 (suppl; abstr 4546).
<http://meetinglibrary.asco.org/content/94426-114>
391. Motzer, R.J., *et al.* Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*, 2013. 14: 552.
<https://www.ncbi.nlm.nih.gov/pubmed/23598172>
392. Hutson, T.E., *et al.* Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol*, 2013. 14: 1287.
<https://www.ncbi.nlm.nih.gov/pubmed/24206640>
393. Choueiri, T.K., *et al.* Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*, 2016. 17: 917.
<https://www.ncbi.nlm.nih.gov/pubmed/27279544>
394. Escudier BJ, *et al.* Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol*, 2010. 28: 2144.
<https://www.ncbi.nlm.nih.gov/pubmed/16860997>
395. Rini, B.I., *et al.* Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol*, 2010. 28: 2137.
<http://www.ncbi.nlm.nih.gov/pubmed/20368558>
396. Rini, B.I., *et al.* Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol*, 2008. 26: 5422.
<https://www.ncbi.nlm.nih.gov/pubmed/18936475>
397. Larkin, J.M., *et al.* Kinase inhibitors in the treatment of renal cell carcinoma. *Crit Rev Oncol Hematol*, 2006. 60: 216.
<https://www.ncbi.nlm.nih.gov/pubmed/16860997>
398. Hutson, T.E., *et al.* Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J Clin Oncol*, 2014. 32: 760.
<https://www.ncbi.nlm.nih.gov/pubmed/24297950>
399. Motzer, R.J., *et al.* Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*, 2008. 372: 449.
<https://www.ncbi.nlm.nih.gov/pubmed/18653228>
400. Motzer, R.J., *et al.* Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer*, 2010. 116: 4256.
<https://www.ncbi.nlm.nih.gov/pubmed/20549832>
401. Calvo, E., *et al.* Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. *Eur J Cancer*, 2012. 48: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/22441644>

402. Bracarda, S., *et al.* Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis. *Br J Cancer*, 2012. 106: 1475.
<https://www.ncbi.nlm.nih.gov/pubmed/22441644>
403. Motzer R.J., *et al.* Record-3: Phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2013 31.
<http://meetinglibrary.asco.org/content/113103-132>
404. Motzer R., *et al.* Phase 3 trial of dovitinib vs sorafenib in patients with metastatic renal cell carcinoma after 1 prior VEGF pathway-targeted and 1 prior mTOR inhibitor therapy. *Eur J Cancer*, 2013. 49: abstract 34. [No abstract available].
405. Bukowski, R.M., *et al.* Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. *J Clin Oncol*, 2007. 25: 4536.
<https://www.ncbi.nlm.nih.gov/pubmed/17876014>
406. Negrier, S., *et al.* Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. *Lancet Oncol*, 2011. 12: 673.
<https://www.ncbi.nlm.nih.gov/pubmed/21664867>
407. McDermott D.F., *et al.* The BEST trial (E2804): A randomized phase II study of VEGF, RAF kinase, and mTOR combination targeted therapy (CTT) with bevacizumab (bev), sorafenib (sor), and temsirolimus (tem) in advanced renal cell carcinoma (RCC). *J Clin Oncol* 31, 2013 (suppl 6; abstr 345), 2013. 31.
<http://meetinglibrary.asco.org/content/107093-134>
408. Rini, B.I., *et al.* Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. *J Clin Oncol*, 2014. 32: 752.
<https://www.ncbi.nlm.nih.gov/pubmed/24297945>
409. Ravaud A, *et al.* Randomized phase II study of first-line everolimus (EVE) + bevacizumab (BEV) versus interferon alfa-2A (IFN) + BEV in patients (pts) with metastatic renal cell carcinoma (MRCC): RECORD-2., in The Annual Meeting of the European Society for Medical Oncology 2012, ESMO: (Vienna, Austria).
<http://oncologypro.esmo.org/Meeting-Resources/ESMO-2012/Randomized-phase-II-study-of-first-line-everolimus-EVE-bevacizumab-BEV-versus-interferon-alfa-2a-IFN-BEV-in-patients-pts-with-metastatic-renal-cell-carcinoma-mRCC-record-2>
410. Motzer, R.J., *et al.* Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol*, 2015. 16: 1473.
<https://www.ncbi.nlm.nih.gov/pubmed/26482279>
411. Gore, M.E., *et al.* Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol*, 2009. 10: 757.
<https://www.ncbi.nlm.nih.gov/pubmed/19615940>
412. Sánchez P, *et al.* Non-clear cell advanced kidney cancer: is there a gold standard? *Anticancer Drugs* 2011. 22 S9.
<https://www.ncbi.nlm.nih.gov/pubmed/21173605>
413. Koh, Y., *et al.* Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. *Ann Oncol*, 2013. 24: 1026.
<https://www.ncbi.nlm.nih.gov/pubmed/23180114>
414. Tannir, N.M., *et al.* A phase 2 trial of sunitinib in patients with advanced non-clear cell renal cell carcinoma. *Eur Urol*, 2012. 62: 1013.
<https://www.ncbi.nlm.nih.gov/pubmed/22771265>
415. Ravaud A, *et al.* First-line sunitinib in type I and II papillary renal cell carcinoma (PRCC): SUPAP, a phase II study of the French Genito-Urinary Group (GETUG) and the Group of Early Phase trials (GEP) *J. Clin Oncol*, 2009. Vol 27, No 15S: 5146.
<http://meeting.ascopubs.org/cgi/content/short/27/15S/5146>
416. Escudier BJ, *et al.* Open-label phase II trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer*, 2016. Volume 49 Supplement 2, 2013.
<https://www.ncbi.nlm.nih.gov/pubmed/27680407>
417. Choueiri, T.K., *et al.* Phase II and Biomarker Study of the Dual MET/VEGFR2 Inhibitor Foretinib in Patients With Papillary Renal Cell Carcinoma. *J Clin Oncol*, 2013. 31: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/23213094>

418. Tannir N.M., *et al.* Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (The ESPN Trial): A multicenter randomized phase 2 trial. *J Clin Oncol* 2014. 32. <http://meetinglibrary.asco.org/content/134866-144>
419. Armstrong AJ, *et al.* Final clinical results of a randomized phase II international trial of everolimus vs. sunitinib in patients with metastatic non-clear cell renal cell carcinoma (ASPEN). *J Clin Oncol*, 2015. 33. <http://meetinglibrary.asco.org/content/147311-156>
420. Fernández-Pello, S., *et al.* A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Nonclear Cell Renal Cell Carcinoma. *Eur Urol*, 2017. 71: 426. <https://www.ncbi.nlm.nih.gov/pubmed/27939075>
421. Kreshover, J.E., *et al.* Renal cell recurrence for T1 tumors after laparoscopic partial nephrectomy. *J Endourol*, 2013. 27: 1468. <https://www.ncbi.nlm.nih.gov/pubmed/24074156>
422. Wah, T.M., *et al.* Radiofrequency ablation (RFA) of renal cell carcinoma (RCC): experience in 200 tumours. *BJU Int*, 2014. 113: 416. <https://www.ncbi.nlm.nih.gov/pubmed/24053769>
423. Margulis, V., *et al.* Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. *J Urol*, 2009. 181: 2044. <https://www.ncbi.nlm.nih.gov/pubmed/19286220>
424. Beisland, C., *et al.* A prospective risk-stratified follow-up programme for radically treated renal cell carcinoma patients: evaluation after eight years of clinical use. *World J Urol*, 2016. 34: 1087. <https://www.ncbi.nlm.nih.gov/pubmed/26922650>
425. Stewart-Merrill, S.B., *et al.* Oncologic Surveillance After Surgical Resection for Renal Cell Carcinoma: A Novel Risk-Based Approach. *J Clin Oncol*, 2015. 33: 4151. <https://www.ncbi.nlm.nih.gov/pubmed/26351352>
426. Pettus, J.A., *et al.* Effect of baseline glomerular filtration rate on survival in patients undergoing partial or radical nephrectomy for renal cortical tumors. *Mayo Clin Proc*, 2008. 83: 1101. <https://www.ncbi.nlm.nih.gov/pubmed/18828969>
427. Snow, D.C., *et al.* Rapid communication: chronic renal insufficiency after laparoscopic partial nephrectomy and radical nephrectomy for pathologic t1a lesions. *J Endourol*, 2008. 22: 337. <https://www.ncbi.nlm.nih.gov/pubmed/18257672>
428. Zini, L., *et al.* Radical versus partial nephrectomy: effect on overall and noncancer mortality. *Cancer*, 2009. 115: 1465. <https://www.ncbi.nlm.nih.gov/pubmed/19195042>
429. Thompson, R.H., *et al.* Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol*, 2008. 179: 468. <https://www.ncbi.nlm.nih.gov/pubmed/18076931>
430. Jeldres, C., *et al.* Partial versus radical nephrectomy in patients with adverse clinical or pathologic characteristics. *Urology*, 2009. 73: 1300. <https://www.ncbi.nlm.nih.gov/pubmed/19376568>
431. Bruno, J.J., 2nd, *et al.* Renal cell carcinoma local recurrences: impact of surgical treatment and concomitant metastasis on survival. *BJU Int*, 2006. 97: 933. <https://www.ncbi.nlm.nih.gov/pubmed/16643473>
432. Sandhu, S.S., *et al.* Surgical excision of isolated renal-bed recurrence after radical nephrectomy for renal cell carcinoma. *BJU Int*, 2005. 95: 522. <https://www.ncbi.nlm.nih.gov/pubmed/15705072>
433. Bani-Hani, A.H., *et al.* Associations with contralateral recurrence following nephrectomy for renal cell carcinoma using a cohort of 2,352 patients. *J Urol*, 2005. 173: 391. <https://www.ncbi.nlm.nih.gov/pubmed/15643178>
434. Lam, J.S., *et al.* Renal cell carcinoma 2005: new frontiers in staging, prognostication and targeted molecular therapy. *J Urol*, 2005. 173: 1853. <https://www.ncbi.nlm.nih.gov/pubmed/15879764>
435. Scoll, B.J., *et al.* Age, tumor size and relative survival of patients with localized renal cell carcinoma: a surveillance, epidemiology and end results analysis. *J Urol*, 2009. 181: 506. <https://www.ncbi.nlm.nih.gov/pubmed/19084868>
436. Doornweerd, B.H., *et al.* Chest X-ray in the follow-up of renal cell carcinoma. *World J Urol*, 2014. 32: 1015. <https://www.ncbi.nlm.nih.gov/pubmed/24096433>

437. McDonald, J.S., *et al.* Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. *Radiology*, 2013. 267: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/23319662>
438. Patard, J.J., *et al.* Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol*, 2004. 171: 2181.
<https://www.ncbi.nlm.nih.gov/pubmed/15126781>
439. Kattan, M.W., *et al.* A postoperative prognostic nomogram for renal cell carcinoma. *J Urol*, 2001. 166: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/11435824>
440. Lam, J.S., *et al.* Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. *J Urol*, 2005. 174: 466.
<https://www.ncbi.nlm.nih.gov/pubmed/16006866>
441. Cindolo, L., *et al.* Comparison of predictive accuracy of four prognostic models for nonmetastatic renal cell carcinoma after nephrectomy: a multicenter European study. *Cancer*, 2005. 104: 1362.
<https://www.ncbi.nlm.nih.gov/pubmed/16116599>
442. Skolarikos, A., *et al.* A review on follow-up strategies for renal cell carcinoma after nephrectomy. *Eur Urol*, 2007. 51: 1490.
<https://www.ncbi.nlm.nih.gov/pubmed/17229521>
443. Chin, A.I., *et al.* Surveillance strategies for renal cell carcinoma patients following nephrectomy. *Rev Urol*, 2006. 8: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/16985554>
444. Ravaud, A., *et al.* Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. *N Engl J Med*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27718781>

10. CONFLICT OF INTEREST

All members of the Renal Cell Cancer working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <https://uroweb.org/guideline/renal-cell-carcinoma/?type=panel/>.

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EAU Guidelines on Testicular Cancer

P. Albers (Chair), W. Albrecht, F. Algaba,
C. Bokemeyer, G. Cohn-Cedermark, K. Fizazi,
A. Horwich, M.P. Laguna, N. Nicolai, J. Oldenburg

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1. INTRODUCTION

1.1 Aim and objectives

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients with cancer of the testis. Testicular cancer represents 5% of urological tumours affecting mostly younger males. This document addresses germ-cell tumours and sex cord/gonadal stromal tumours.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The European Association of Urology (EAU) Guidelines Panel on Testicular Cancer consists of a multidisciplinary group of clinicians including, urologists, oncologists, radiotherapists and a pathologist. Members of this panel have been selected, based on their expertise, to represent the professionals treating patients suspected of having testis cancer. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guideline/testicular-cancer/>.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available as are a number of translations of all versions of the EAU Testicular Cancer Guidelines. All documents can be viewed on the EAU website: <http://www.uroweb.org/guideline/testicular-cancer/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The European Association of Urology (EAU) published the first guidelines on Testicular Cancer in 2001. Since 2008, the Testicular Cancer Guidelines contain a separate chapter on testicular stromal tumours. This document presents a limited update of the 2016 publication. Review papers have been published in the society's scientific journal European Urology, the latest version dating to 2015 [1].

1.4.2 Summary of changes

For the 2017 Testicular Cancer Guidelines, new references have been added throughout the 2017 Testicular Cancer Guidelines document. Key changes in this publication include:

- Section 5.7 - Germ cell tumours histological markers. This is a new table.
- Table 7.2 - An alternative schedule for salvage chemotherapy has been included.
- Chapter 8 - Section 8.1 Rationale for follow up, has been completely replaced, including three new tables, based on the findings of an ESMO Testis Cancer Consensus Committee.

Recommendations were changed in the following sections:

5.9 Guidelines for the diagnosis and staging of testicular cancer

Recommendations	GR
Advise patients with a familiar history of testis cancer, as well as their family members, to perform regular testicular self-examination.	A

7.2.2.6 Risk-adapted treatment for clinical stage 1 based on vascular invasion

Stage 1B (pT2-pT4): high risk	GR
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	A*
Offer nerve-sparing RPLND to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	A*

*Upgraded following panel consensus.

7.4.6 Guidelines for the treatment of metastatic germ cell tumours

Recommendations	LE	GR
Initially offer radiotherapy for seminoma CS IIA. When necessary, use chemotherapy as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.	1a	A
Initially offer chemotherapy in seminoma stage CS IIB (BEP x 3 or etoposide, cisplatin (EP) x 4, in good prognosis) as an alternative to radiotherapy.	1a	A

Table 8.1: Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic computed tomography/ magnetic resonance imaging	2 times	2 times	Once at 36 months	Once at 60 months	

Table 8.2: Recommended minimal follow-up for non-seminoma stage I on active surveillance

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times**	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
Abdominopelvic computed tomography/ magnetic resonance imaging	2 times	At 24 months***	Once at 36 months*	Once at 60 months*	

* Recommended by 50% of consensus group members.

**In case of high risk (LVI+) a minority of consensus group members recommended six times.

***In case of high risk (LVI+) a majority of consensus group members recommended an additional CT at eighteen months.

Table 8.3: Recommended minimal follow up after adjuvant treatment or complete remission for advanced disease (excluded: poor prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic computed tomography/ magnetic resonance imaging	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	*	*	*	*	

*Same time points as abdomino-pelvic CT/MRI in case of pulmonary metastases at diagnosis.

**In case of teratoma in resected residual disease: patient should remain with uro-oncologist.

2. METHODS

For the Germ Cell Tumour section, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies) published in the English language. The search was restricted to articles published between Jan 1st 2010 and September 28th, 2016. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 1,735 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available on line:

<https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications>.

For Testicular Stromal tumours additional literature has been added. A formal scoping search covering the time frame between Jan 1st, 2009 and October 13th, 2014 was performed, without restrictions applied on data level.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [2]. Additional information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.1 Review

This document was subjected to peer review prior to publication in 2015.

2.2 Future goals

The results of an ongoing systematic review, performed using standard Cochrane systematic review methodology, will be included in 2018 update of the Testicular Cancer Guidelines: <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>.

Ongoing systematic review:

- Tumour size and rete testis invasion in the radical orchiectomy specimens of patients with clinical stage I seminoma testis undergoing active surveillance risk factors for developing disease recurrence [3].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Testicular cancer represents 1% of male neoplasms and 5% of urological tumours, with 3-10 new cases occurring per 100,000 males/per year in Western societies [4, 5]. Its incidence has been increasing during the last decades especially in industrialised countries [5-7]. Data from the Surveillance Epidemiology and End Results programme (1992 to 2011) show a continuing increased risk among Caucasian men in the USA for seminoma [8].

At diagnosis, 1-2% of cases are bilateral and the predominant histology is germ cell tumour (90-95% of cases) [4]. Peak incidence is in the third decade of life for non-seminoma, and in the fourth decade for pure seminoma.

Testicular cancers (TC) show excellent cure rates based on, their chemosensitivity especially to cisplatin-based chemotherapy [9], careful staging at diagnosis, adequate early treatment based on a multidisciplinary approach and strict follow-up and salvage therapies. A decrease in the meantime of delay to diagnosis and treatment has been observed. Although early stages can be successfully treated in a non-reference centre, the relapse rate is higher [10, 11]. In poor prognosis non-seminomatous germ cell tumours (NSGCT), overall survival (OS) within a clinical trial depends on the number of patients treated at the participating centre (worse if < 5 patients enrolled) [12]. In the same context, the frequency of post-chemotherapy residual tumour resection is associated with peri-operative mortality and OS [13, 14]. Establishment of second-opinion clinics for testicular cancer patients may prevent over- and under-treatment [15].

Genetic changes have been described in patients with TC. A specific genetic marker, an isochromosome of the short arm of chromosome 12 - i(12p) - has been described in all histological types of germ cell tumours [16] and in germ cell neoplasia *in situ* (GCNIS). Alterations in the p53 locus have been identified in 66% of cases of GCNIS [17] and association between genetic polymorphism in the PTEN tumours suppressor gene and risk of testicular germ cell tumours (TGCT) has been recently described [18]. A deregulation in the pluripotent programme of foetal germ cells (identified by specific markers, M2A, C-KIT and OCT4/NANOG) is likely responsible for the development of GCNIS and germ cell neoplasia. In line with this, significant association between markers at loci 4q22.2, 7p22.3, 16q22.3 and 17q22, all of which encoding proteins for male cell germ development and susceptibility for TGCT has been described [19]. There is overlap in the development to seminoma and embryonal carcinoma as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma [20, 21].

Epidemiological risk factors for the development of testicular tumours are components of the testicular dysgenesis syndrome (i.e. cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility) [22, 23], familial history of testicular tumours among first-grade relatives and the presence of a contralateral tumour or GCNIS [16, 22, 24-28]. A recent systematic review confirmed the association between height and TGCT with an odds ratio (OR) of 1.13 per 5 cm increase in height [29].

3.2 Pathological classification

The recommended pathological classification shown below is based on the 2016 update of the World Health Organization (WHO) pathological classification [30].

1. Germ cell tumours

- Derived from germ cell neoplasia *in situ* (GCNIS)
- Germ cell neoplasia *in situ*

Seminoma

- Embryonal carcinoma
- Yolk sac tumour, post-pubertal type
- Trophoblastic tumours
- Teratoma, post-pubertal type
- Teratoma with somatic-type malignancies
- Mixed germ cell tumours

2. Germ cell tumours unrelated to GCNIS

- Spermatocytic tumour
- Yolk sac tumour, pre-pubertal type
- Mixed germ cell tumour, pre-pubertal type

3. Sex cord/stromal tumours

- Leydig cell tumour
 - Malignant Leydig cell tumour
- Sertoli cell tumour
 - Malignant Sertoli cell tumour
 - Large cell calcifying Sertoli cell tumour
 - Intratubular large cell hyalinising Sertoli cell neoplasia
- Granulosa cell tumour
 - Adult type
 - Juvenile type
- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours
 - Mixed
 - Unclassified
- Tumours containing both germ cell and sex cord/gonadal stromal
 - Gonadoblastoma

4. Miscellaneous non-specific stromal tumours

- Ovarian epithelial tumours
- Tumours of the collecting ducts and rete testis
 - Adenoma
 - Carcinoma

- Tumours of paratesticular structures
 - Adenomatoid tumour
 - Mesothelioma (epithelioid, biphasic)
 - Epididymal tumours
- Cystadenoma of the epididymis
- Papillary cystadenoma
- Adenocarcinoma of the epididymis
- Mesenchymal tumours of the spermatic cord and testicular adnexae.

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Diagnostic tools

To determine the presence of macroscopic or occult metastatic disease, the half-life kinetics of serum tumour markers as well as the presence of nodal or visceral metastases need to be assessed. Consequently, it is mandatory to assess:

- the pre- and post-orchietomy half-life kinetics of serum tumour markers;
- the status of retroperitoneal and supraclavicular lymph nodes, bone and liver;
- the presence or absence of mediastinal nodal involvement and lung metastases;
- the status of brain and bone in cases of suspicious symptoms or high-risk disease, e.g. poor International Germ Cell Cancer Collaborative Group (IGCCCG) risk group, high human chorionic gonadotropin (hCG) and/or multiple pulmonary metastases.

The minimum mandatory tests are:

- serial blood sampling;
- abdominopelvic and chest computed tomography (CT).

4.2 Serum tumour markers: post-orchietomy half-life kinetics

The mean serum half-life of AFP and hCG is five to seven days and two to three days, respectively [31]. Tumour markers need to be re-evaluated after orchietomy to determine half-life kinetics. Marker decline in patients with clinical stage (CS) I disease should be assessed until normalisation has occurred. Markers before the start of chemotherapy are important to classify the patient according to the IGCCCG risk classification [32]. The persistence of elevated serum tumour markers after orchietomy might indicate the presence of metastatic disease (macro- or microscopically), while the normalisation of marker levels after orchietomy does not rule out the presence of tumour metastases. During chemotherapy, the markers should decline; persistence has an adverse prognostic value [33, 34]. Slow marker decline in patients with poor prognosis during the first cycle of standard bleomycin, etoposide and cisplatin (BEP) chemotherapy can be used as an indication for early chemotherapy dose intensification [35].

4.3 Retroperitoneal, mediastinal and supraclavicular lymph nodes and viscera

Retroperitoneal and mediastinal lymph nodes are best assessed by CT. The supraclavicular nodes are best assessed by physical examination followed by CT in cases of suspicion.

Abdominopelvic CT offers a sensitivity of 70-80% in determining the state of the retroperitoneal nodes. Its accuracy depends on the size and shape of the nodes; sensitivity and the negative predictive value increase using a 3 mm threshold to define metastatic nodes in the landing zones [36]. Those figures decrease slightly in stages I and II [37, 38], with a rate of understaging of 25-30% [39].

Magnetic resonance imaging (MRI) produces similar results to CT in the detection of retroperitoneal nodal enlargement [40, 41]. Again, the main objections to its routine use are its high cost and limited availability. Nevertheless, MRI can be helpful when abdominopelvic CT or ultrasound (US) are inconclusive [40], when CT is contraindicated because of allergy to contrast media containing iodine, or when the physician or the patient are concerned about radiation dose. MRI is an optional test, and there are currently no indications for its systematic use in the staging of TC.

A chest CT is the most sensitive way to evaluate the thorax and mediastinal nodes. This exploration is recommended in all patients with TC as up to 10% of cases can present with small subpleural nodes that are not visible on an X-ray [42]. A CT has high sensitivity, but low specificity.

There is no evidence to support the use of fluorodeoxyglucose-positron emission tomography (PET) (FDG-PET) in the staging of testis cancer [43, 44]. It is recommended in the follow up of patients with seminoma with a residual mass larger than 3 cm and should not be performed before eight weeks after

completing the last cycle of chemotherapy in order to decide on watchful waiting or active treatment [45, 46]. Fluorodeoxyglucose-PET is not recommended in the re-staging of patients with NSGCT after chemotherapy [47].

Other examinations, such as brain or spinal CT, bone scan or liver US, should be performed if there is suspicion of metastases to these organs. A CT or MRI of the brain is advisable in patients with NSGCT, multiple lung metastases and poor prognosis IGCCG risk group (e.g. high beta-hCG values). Table 4.1 shows the recommended tests at staging.

Table 4.1: Recommended tests for staging at diagnosis

Test	Recommendation	GR
Serum tumour markers	Alpha-fetoprotein human chorionic gonadotrophin (hCG) Lactate dehydrogenase	A
Abdominopelvic computed tomography (CT)	All patients	A
Chest CT	All patients	A
Testis ultrasound (bilateral)	All patients	A
Bone scan or magnetic resonance imaging (MRI) columna	In case of symptoms	
Brain scan (CT/MRI)	In case of symptoms and patients with metastatic disease with multiple lung metastases and/or high beta-hCG values.	
Further investigations		
Fertility investigations: Total testosterone Luteinising hormone Follicle-stimulating hormone Semen analysis		B
Discuss sperm banking with all men prior to starting treatment for testicular cancer.		A

4.4 Staging and prognostic classifications

The staging system recommended in these guidelines is the 2017 Tumour, Node, Metastasis (TNM) of the International Union Against Cancer (UICC) (Table 4.2) [30]. This includes:

- determination of the anatomical extent of disease;
- assessment of serum tumour markers, including nadir values of hCG, AFP and LDH after orchiectomy (S category);
- definition of regional nodes;
- N-category modifications related to node size.

Table 4.2: TNM classification for testicular cancer (UICC, 2017, 8th edn. [30])

pT -	Primary Tumour ¹
pTX	Primary tumour cannot be assessed (see note 1)
pT0	No evidence of primary tumour (e.g. histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma <i>in situ</i>)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis*
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N -	Regional Lymph Nodes - Clinical
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension.

N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
Pn - Regional Lymph Nodes - Pathological			
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M - Distant Metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
	M1a Non-regional lymph node(s) or lung metastasis		
	M1b Distant metastasis other than non-regional lymph nodes and lung		
S - Serum Tumour Markers			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	hCG (mIU/mL)	AFP (ng/mL)
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal for the LDH assay.

LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.

*AJCC subdivides T1 by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension.

¹ Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

According to the 2009 TNM classification, stage I testicular cancer includes the following substages:

Stage grouping				
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any patient/TX	N0	M0	S1-3
Stage II	Any patient/TX	N1-N3	M0	SX
Stage IIA	Any patient/TX	N1	M0	S0
	Any patient/TX	N1	M0	S1
Stage IIB	Any patient/TX	N2	M0	S0
	Any patient/TX	N2	M0	S1
Stage II	Any patient/TX	N3	M0	S0
	Any patient/TX	N3	M0	S1
Stage III	Any patient/TX	Any N	M1a	SX
Stage IIIA	Any patient/TX	Any N	M1a	S0
	Any patient/TX	Any N	M1a	S1
Stage IIIB	Any patient/TX	N1-N3	M0	S2
	Any patient/TX	Any N	M1a	S2
Stage IIIC	Any patient/TX	N1-N3	M0	S3
	Any patient/TX	Any N	M1a	S3
	Any patient/TX	Any N	M1b	Any S

Stage IA	patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchietomy serum tumour marker levels within normal limits. Marker decline in patients with CS I disease should be assessed until normalisation.
Stage IB	patients have a more locally invasive primary tumour, but no sign of metastatic disease.
Stage IS	patients have persistently elevated (and usually increasing) serum tumour marker levels after orchietomy, indicating subclinical metastatic disease (or possibly a second germ cell tumour in the remaining testis).

In large population-based patient series, 75-80% of seminoma patients, and about 55% of patients with NSGCT cancer have stage I disease at diagnosis [48, 49]. True stage IS (persistently elevated or increasing serum marker levels after orchietomy) is found in about 5% of non-seminoma patients.

In 1997, the IGCCCG defined a prognostic factor-based staging system for metastatic testis tumours based on identification of clinically independent adverse factors. This staging system has been incorporated into the TNM Classification and uses histology, location of the primary tumour, location of metastases and pre-chemotherapy marker levels in serum as prognostic factors to categorise patients into 'good', 'intermediate' or 'poor' prognosis (Table 4.3) [33].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer
(International Germ Cell Cancer Collaborative Group [50])*

Good-prognosis group	
<i>Non-seminoma (56% of cases)</i> 5-year PFS 89% 5-year survival 92%	<i>All of the following criteria:</i> <ul style="list-style-type: none"> • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
<i>Seminoma (90% of cases)</i> 5-year PFS 82% 5-year survival 86%	<i>All of the following criteria:</i> <ul style="list-style-type: none"> • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate prognosis group	
<i>Non-seminoma (28% of cases)</i> 5-year PFS 75% 5-year survival 80%	<i>Any of the following criteria:</i> <ul style="list-style-type: none"> • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
<i>Seminoma (10% of cases)</i> 5-year PFS 67% 5-year survival 72%	<i>All of the following criteria:</i> <ul style="list-style-type: none"> • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor prognosis group	
<i>Non-seminoma (16% of cases)</i> 5-year PFS 41% 5-year survival 48%	<i>Any of the following criteria:</i> <ul style="list-style-type: none"> • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
<i>Seminoma</i>	No patients classified as poor prognosis

*Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day). PFS = progression-free survival; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase.

5. DIAGNOSTIC EVALUATION

5.1 Clinical examination

Testicular cancer usually presents as a painless, unilateral testicular scrotal mass, as a casual US finding or is revealed by a scrotal trauma [51]. Scrotal pain may be the first symptom in 20% of cases and it is present in up to 27% of patients with TC [51, 52]. Gynaecomastia appears in 7% of cases (more common in non-seminomatous tumours). Back and flank pain due to metastasis is present in about 11% of cases [52].

Diagnosis is delayed in around 10% of cases of testicular tumour that mimic orchioepididymitis [52], physical examination reveals the features of the mass and must always be carried out together with a general examination to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. Ultrasound must be performed in any doubtful case. A correct diagnosis must be established in all patients with an intrascrotal mass [53].

5.2 Imaging of the testis

Currently, US is used to confirm the presence of a testicular mass and explore the contralateral testis. Ultrasound sensitivity is almost 100%, and US has an important role in determining whether a mass is intra- or extra-testicular [54]. Ultrasound is an inexpensive test and should be performed even in the presence of clinically evident testicular tumour [55].

Ultrasound of the testis should be performed in young men with retroperitoneal or visceral masses and/or elevated serum hCG or AFP and/or consulting for fertility problems and without a palpable testicular mass [56, 57].

Magnetic resonance imaging of the scrotum offers higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for diagnosis [54, 58].

5.3 Serum tumour markers at diagnosis

Serum tumour markers are prognostic factors and contribute to diagnosis and staging [59]. The following markers should be determined before, and 5-7 days after, orchiectomy:

- alpha-fetoprotein (produced by yolk sac cells);
- human chorionic gonadotrophin (expression of trophoblasts);
- lactate dehydrogenase.

Tumour markers are of value for diagnosis (before orchiectomy) as well as for prognosis (after orchiectomy). They are increased in approximately every second patient with TC [51, 60]. Alpha-fetoprotein and hCG are increased in 50-70% and in 40-60% of patients with NSGCT, respectively. About 90% of NSGCT present with a rise in one or both of the markers. Up to 30% of seminomas can present or develop an elevated hCG level during the course of the disease [31].

Lactate dehydrogenase is a less specific marker, its concentration being proportional to tumour volume. Its level may be elevated in 80% of patients with advanced TC [31]. Of note, negative marker levels do not exclude the diagnosis of a germ cell tumour. Placental alkaline phosphatase (PLAP), is an optional marker in monitoring patients with pure seminoma, but not recommended in smokers [61].

Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research. There is preliminary evidence that some micro-RNAs (miRNA 371-373) may be of diagnostic value in the future [62].

5.4 Inguinal exploration and orchiectomy

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorisation of the testis within its tunics. Orchiectomy with division of the spermatic cord at the internal inguinal ring must be performed if a malignant tumour is found. If the diagnosis is not clear, a testicular biopsy (and enucleation of the intraparenchymal tumour) is taken for frozen (fresh tissue) section histological examination. Even though only limited data are available, it has been shown that during orchiectomy, a testicular prosthesis can be inserted without increased infectious complications or rejection rates [63].

In cases of life-threatening disseminated disease, lifesaving chemotherapy should be given up-front, especially when the clinical picture is very likely TC and/or tumour markers are increased. Orchiectomy may be delayed until clinical stabilisation occurs or in combination with resection of residual lesions.

5.5 Organ-sparing surgery

Although organ-sparing surgery is not indicated in the presence of non-tumoural contralateral testis, it can be attempted in special cases with all the necessary precautions. In synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a tumour in a solitary testis with normal pre-operative testosterone levels, organ preserving surgery can be performed when tumour volume is less than approximately 30% of

the testicular volume and surgical rules are respected. In those cases, the rate of associated GCNIS is high (at least up to 82%) (see Section 5.7.)

5.6 Pathological examination of the testis

Mandatory pathological requirements:

- macroscopic features: side, testis size, maximum tumour size, and macroscopic features of the epididymis, spermatic cord, and tunica vaginalis;
- sampling: a 1 cm² section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis, with selection of suspected areas;
- at least one proximal and one distal section of spermatic cord plus any suspected area;
- microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage) according to WHO 2004 [64];
 - presence or absence of peri-tumoural venous and/or lymphatic invasion;
 - presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion;
 - presence or absence of GCNIS in non-tumour parenchyma.
- pT category according to TNM 2016 [30];
- immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and hCG.

Advisable immunohistochemical markers, in cases of doubt, are:

- in seminoma: cytokeratins (CAM 5.2), PLAP, c-kit;
- in ITGCN: PLAP, c-kit;
- other advisable markers: chromogranin A (Cg A), Ki-67 (MIB-1).

5.7 Germ cell tumours histological markers

Marker	GCNIS	Seminoma	Post-puberal yolk sac tumour	Embryonal Carcinoma	Tropho-blastic Cyto	Tropho-blastic Syncytio	Sperma-tocytic tumour	Pre-puberal yolk sac tumour	Sex cord gonadal stromal tumours
OCT3/4	100%	100%	-	90%	-	--	-	-	-
SALL 4	90%	100%	90%	90%	+	-	50-90% (weak)	100%	-
Glypican3	-	-	100%	8%	100% (irregular)	100% (irregular)	-	-	-
CD30	-	< 10%	< 10%	100%	-	-	-	-	-
AFP	-	-	80%	33%	-	-	-	-	-
β-hCG	-	-	-	-	-	100%	-	-	-
CD117	100%	90/100%	60% (focal)	-	-	-	+/- (weak)	-	-
PLAP	100%	86/95%	53%	86%	+/-	100%	-	-	-
α-inhibin	-	-	-	-	-	+/-	-	+	Sertoli; 30-50% Leydig; 100%
Calretinin	-	-	-	-	-	-	-	-	100%
AE1/AE3	-	20/36%	+ (focal)	95% (weak)	+/-	+/-	-	-	Sertoli: 64% Leydig: 42%
EMA	-	2%	5%	2%	-	46%	-	-	+/-
CEA	-	-	11%	-	-	25%	-	-	-
GATA 3	-	-	100%	40% (focal)	+	100%	-	-	-
hPL	-	-	-	-	-	+	-	-	-
CgA	-	-	-	-	-	-	-	-	Sertoli: 82% Leydig: 92%

Synapto									Sertoli: 45%
									Leydig: 70%
p63	-	-	-	-	+	-	-		-

OCT3/4 = homeodomain transcription factor of the POU family; SALL 4 = transcription factor encoded by a member of the Spalt-like (SALL) gene family; Glypican 3 (GPC3) = a membrane-bound heparin sulphate proteoglycan; CD30 = immunohistochemical marker; AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; CD117(c-KIT) = immunohistochemical marker; PLAP = placental alkaline phosphatase; α -inhibin = peptide hormone; Calretinin = 29 kD calcium-binding protein; AE1/AE3 = cytokeratins; EMA = epithelial membrane antigen; CEA = carcinoembryonic antigen; GATA 3 = transcription factor; hPL = human placental lactogen; CgA = Chromogranin A; Synapto = neuroendocrine markers; p63 = transformation-related protein 63.

5.8 Diagnosis and treatment of germ cell neoplasia *in situ* (GCNIS)

Contralateral biopsy has been advocated to rule out the presence of GCNIS [65]. Although routine policy in some countries [66], the low incidence of GCNIS and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) [67, 68] the morbidity of GCNIS treatment, and the fact that most of metachronous tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy in all patients [69, 70].

It is still difficult to reach a consensus on whether the existence of contralateral GCNIS must be identified in all cases. However, biopsy of the contralateral testis should be offered to patients at high risk for contralateral GCNIS, i.e. testicular volume < 12 mL, a history of cryptorchidism or poor spermatogenesis (Johnson Score 1-3). A contralateral biopsy is not necessary in patients older than 40 years without risk factors [36, 49, 71-73]. A double biopsy increases sensitivity [72]. Patients should be informed that a testicular tumour may arise in spite of a negative biopsy [74].

Once GCNIS is diagnosed, local radiotherapy (16-20 Gy in fractions of 2 Gy) is the treatment of choice in the case of a solitary testis. Testicular radiotherapy in a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [37, 69, 75, 76]. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US [72]. Chemotherapy is significantly less effective and the cure rates are dose-dependent [77].

If GCNIS is diagnosed and the contralateral testis is healthy, the options for management are orchiectomy or close observation (with a 5-year risk of developing TC of 50%) [78].

5.9 Screening

There are no high level evidence studies proving the advantages of screening programmes [79], but it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, and especially in patients with a family history of testis cancer, family members and the patient should be informed about the importance of physical self-examination [80].

5.10 Guidelines for the diagnosis and staging of testicular cancer

Recommendations	GR
Perform testicular ultrasound in all patients with suspicion of testicular cancer.	A
Offer biopsy of the contralateral testis and discuss its consequences with patients at high risk for contralateral germ cell neoplasia <i>in situ</i> .	A
Perform orchiectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, start chemotherapy before orchiectomy.	A
Perform serum determination of tumour markers (alpha-fetoprotein, human chorionic gonadotrophin, and lactate dehydrogenase), both before and five-seven days after orchiectomy for staging and prognostic reasons.	A
Assess the state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera in testicular cancer.	A
Advise patients with a familiar history of testis cancer, as well as their family members, to perform regular testicular self-examination.	A

6. PROGNOSIS

6.1 Risk factors for metastatic relapse in clinical stage I

Retrospectively, for seminoma stage I, tumour size (> 4 cm) and invasion of the rete testis have been identified as predictors for relapse in a pooled analysis [81]. The absence of both factors indicated a low recurrence rate (6%) [82]. Although the original model was not found to apply in a further retrospective report [83], other prospective series [84, 85, 96] confirm the prognostic importance of tumour size and stromal invasion of the rete testis.

With modern imaging, CS I patients with seminoma face a risk of occult metastasis, independent of risk factors, of < 15% in all recently published series.

For non-seminoma stage I, vascular invasion of the primary tumour in blood or lymphatic vessels is the most important predictor of occult metastatic disease. The proliferation rate, as well as the percentage of embryonal carcinoma, are additional predictors that improve upon the positive and negative predictive value of vascular invasion [86]. Whether the absence of teratoma (as qualitative data, as opposed to the more subjective assessment of percentage of embryonal carcinoma) can independently complement vascular invasion as a predictive factor of relapse requires validation [87].

The significant prognostic pathological risk factors for stage I TC are listed in Table 6.1.

Table 6.1: Risk factors for occult metastatic disease in stage I testicular cancer

	For seminoma	For non-seminoma
Pathological (for stage I)		
Histopathological type	<ul style="list-style-type: none"> • Tumour size (> 4 cm) • Invasion of the rete testis 	<ul style="list-style-type: none"> • Vascular/lymphatic in or peritumoural invasion • Proliferation rate > 70% • Percentage of embryonal carcinoma > 50%

7. DISEASE MANAGEMENT

7.1 Impact on fertility and fertility-associated issues

Sperm abnormalities are frequently found in patients with testis tumours. Furthermore, chemotherapy and radiation treatment can additionally impair fertility, however long-term infertility is rare after radiotherapy and dose-cumulative-dependant after chemotherapy [88, 89]. In patients in the reproductive age group, pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and follicle stimulating hormone [FSH] levels) should be performed, and semen analysis and cryopreservation should be offered. If cryopreservation is desired, it should preferably be performed before orchiectomy, but in any case prior to chemotherapy [75, 88-91]. In cases of bilateral orchiectomy or low testosterone levels after treatment of GCNIS, life-long testosterone supplementation is necessary [92]. Patients with unilateral or bilateral orchiectomy should be offered a testicular prosthesis [93]. For more detailed information, the reader is referred to the EAU Male Infertility Guidelines [94].

7.2 Stage I Germ cell tumours

7.2.1 Stage I seminoma

After modern staging procedures, less than 15% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone [83, 95-97].

The decision regarding adjuvant treatment should always be based on a thorough discussion with the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

7.2.1.1 Surveillance

Several prospective non-randomised surveillance studies have been conducted during the past decade, the largest study from Canada with > 1,500 patients [98]. Previous analyses from four studies showed an actuarial five-year relapse-free rate of 82.3%. The Princess Margaret Hospital series (n = 1,559) showed an overall relapse rate in unselected patients of 16.8%. The actuarial relapse rate is in the order of 15-20% at five years,

and most of the relapses are first detected in infra-diaphragmatic lymph nodes [99].

In patients with low risk (tumour size < 4 cm and no rete testis invasion), the recurrence under surveillance is as low as 6% [85]. Chemotherapy, according to the IGCCCG classification, is a possible treatment for seminoma relapse under surveillance. However, 70% of patients with relapse are suitable for treatment with radiotherapy alone because of small volume disease at the time of recurrence. Patients who relapse after salvage radiotherapy can be effectively treated with chemotherapy [100]. The combination of carboplatin chemotherapy and modern radiotherapy for treatment of low stage seminoma relapse (IIA/IIB) is under investigation.

The overall cancer-specific survival (CSS) rate reported under surveillance performed by experienced centres is 97-100% for seminoma stage I [99, 100]. The main drawback of surveillance is the need for more intensive follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes.

7.2.1.2 Adjuvant chemotherapy

A joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC), which compared one cycle of carboplatin area under curve (AUC) 7 with adjuvant radiotherapy, did not show a significant difference with regard to recurrence rate, time to recurrence and survival after a median follow up of four years [101-103]. Therefore, adjuvant carboplatin therapy using a dosage of one course of AUC 7 is an alternative to radiotherapy or surveillance in stage I seminoma [99, 101-103]. Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1-3% [82, 104]. Long-term data report the recurrence rate after three years after adjuvant carboplatin as 15%. Not all of these patients were cured [105].

7.2.1.3 Adjuvant radiotherapy and risk-adapted treatment

Seminoma cells are extremely radiosensitive. Adjuvant radiotherapy to a para-aortic (PA) field or to a PA and ipsilateral field (PA and ipsilateral iliac nodes), with moderate doses (total 20-24 Gy), will reduce the relapse rate to 1-3% [106-108]. Adjuvant irradiation of supra-diaphragmatic lymph nodes is not indicated.

With regard to the irradiation dose, a large Medical Research Council (MRC) randomised trial of 20 Gy vs. 30 Gy PA radiation in stage I seminoma showed non-inferiority in terms of recurrence rates [107]. The rate of severe radiation induced long-term toxicity is less than 2%. Moderate chronic gastrointestinal (GI) side-effects are seen in about 5% of patients, and moderate acute GI toxicity in about 60% [106]. The main concern surrounding adjuvant radiotherapy is the increased risk of radiation-induced second non-germ cell malignancies [109-111].

A scrotal shield should be considered during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis [109].

7.2.1.4 Risk-adapted treatment

Using tumour size > 4 cm and rete testis invasion, patients with seminoma stage I may be subdivided into a low- and high-risk groups for occult metastatic disease. Patients with and without both risk factors have a 32% and 12% risk of occult disease respectively. These risk factors were introduced through an analysis of retrospective trials [81], and then confirmed in prospective studies [85, 96, 112]. A prospective trial based on one or no risk factors, showed the feasibility of a risk-adapted approach; the group without risk factors were managed with surveillance, whilst the group with both risk factors received two courses of carboplatin, AUC 7. Early data with limited follow up indicated that patients without either risk factor have a very low risk, 6.0% - 15%, of relapse at five years. Patients in the high-risk group treated with two courses of carboplatin experienced a 1.4% - 3.2% relapse rate at mean follow up of 34 months [85, 112].

7.2.1.5 Guidelines for the treatment of stage I seminoma

Recommendations	GR
Offer surveillance as a management option if facilities are available and the patient is compliant.	A*
Offer one course at area under curve (AUC) 7, if carboplatin chemotherapy is considered.	A
Do not perform adjuvant treatment in patients at very low risk (no risk factors).	A
Do not perform radiotherapy as adjuvant treatment.	A

*Upgraded following panel consensus.

7.2.2 NSGCT clinical stage I

Up to 30% of NSGCT patients with CS1 disease have subclinical metastases and will relapse during surveillance. The decision regarding adjuvant treatment should always be based on a thorough discussion with

the patient, taking into account the described advantages and disadvantages, as well as the individual situation of the patient.

7.2.2.1 Surveillance

Improvements in clinical staging and follow-up methods, and the availability of effective salvage treatment with cisplatin-based chemotherapy and post-chemotherapy surgery, have led to studies of only close surveillance after orchiectomy in CS1 NSGCT patients. The largest reports of the surveillance strategy indicate a cumulative relapse rate of about 30%, with 80% of relapses occurring during the first twelve months of follow up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later [114, 115]. Approximately 35% of relapsing patients have normal levels of serum tumour markers at relapse, with 60% of relapses occurring in the retroperitoneum. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.

The somewhat lower relapse rates reported from surveillance studies compared with some series of patients staged by RPLND [116] can be explained by the fact that some patients (presumably at higher risk) are excluded once surveillance is advised. Based on the overall CSS data, surveillance within an experienced surveillance programme can safely be offered to patients with non-risk stratified CSI non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment [117, 118].

7.2.2.2 Adjuvant chemotherapy

Patients with CS1 NSGCT have a 14-48% risk of recurrence within two years after orchiectomy. Adjuvant chemotherapy with two courses of BEP was introduced in 1996 by a prospective MRC trial [119]. Subsequently, adjuvant chemotherapy was mainly given in high-risk patients (vascular invasion present) [119-121]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [119], a relapse rate of only 2.7% was reported, with very little long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not seem to adversely affect fertility or sexual activity [122]. However, the very-long term (> 20 years) side effects of adjuvant chemotherapy in this setting are currently unknown, especially the long-term cardio-vascular effects of chemotherapy [123]. This should be taken into consideration during decision-making.

In 2008, a randomised trial of nerve-sparing RPLND or one course of BEP as adjuvant treatment in CS1 NSGCT without risk-adaptation reported [124]. Adjuvant chemotherapy significantly increased the two-year recurrence-free survival rate to 99.41% (CI: 95.87%, 99.92%) as opposed to surgery, which had a two-year recurrence-free survival rate of 92.37% (CI: 87.21%, 95.50%). The difference was 7.04%, (CI: 2.52%, 11.56%) and, therefore, the main endpoint of the trial was reached. The hazard ratio to experience a tumour recurrence with surgery as opposed to chemotherapy was 7.937, (CI: 1.808, 34.48). Of the 174 patients having received one course of BEP, 43% had high-risk features (> pT1) [124].

A community-based prospective study recommended one course of BEP in LVI+ patients, while LVI- patients chose between surveillance and BEP x 1 [125]. The relapse-rate of the 490 patients who received BEP x 1 at five years was 3.2% for LVI+ patients and 1.6% for LVI- patients. After a median follow up of 8.1 years the relapse rate was 2.3%, 3.4% and 1.3% for all, LVI+, and LVI-, respectively [126]. These numbers imply that > 90% of relapses were prevented by adjuvant chemotherapy and, importantly, no relapses were observed later than 3.3 years. Reduction from two to one cycle of BEP improves the risk-benefit ratio of adjuvant chemotherapy considerably.

In addition, it is important to be aware of slow-growing retroperitoneal teratomas after primary chemotherapy [109]. Until now, only a limited number of patients with long-term follow-up and toxicity data have been reported on [127].

The results of cost analyses comparing surveillance, RPLND and primary chemotherapy show different results among the reported studies, possibly because of differences in intensity and costs related to follow-up procedures [128]. With low frequency follow-up CTs (a surveillance strategy which has been proven to be effective in non-seminoma CS1), the costs of follow up can be considerably reduced [129].

7.2.2.3 Risk-adapted treatment

Risk-adapted treatment is an alternative to surveillance for all patients with CS1 NSGCT. Risk-adapted treatment is based on the risk factor of vascular invasion. Stratifying patients with CS1 NSGCT according to their presumed risk of relapse is a rational option, as several studies have reported similar survival rates and a final cure rate close to 100% with all available treatment options using the risk-stratifying approach [119-121, 125, 126, 130-132].

If the risk-adapted policy is applied, patients with vascular invasion are recommended to undergo adjuvant chemotherapy and patients with absent vascular invasion are recommended a surveillance strategy. In the past, two cycles of BEP have been recommended for adjuvant treatment. In view of the low rates of recurrence (2-3%) and equivalent CSS rates including salvage strategies in large prospective trials with sufficient follow-up, one cycle of BEP is now recommended as adjuvant chemotherapy in patients with vascular invasion.

In cases of relapse after BEP x 1, three courses of BEP are recommended. However, there is not a large body of evidence to support any one specific salvage regimen.

7.2.2.4 Retroperitoneal lymph node dissection

In view of the high CSS rates of surveillance with salvage treatment in cases of relapse and the low relapse rates if adjuvant chemotherapy is chosen, the role of primary diagnostic RPLND has diminished. A randomised phase III trial compared RPLND to BEP x 1 as adjuvant treatment, with a 7% difference in favour of chemotherapy. One course of BEP showed a significantly lower recurrence rate as compared to surgery [124].

When RPLND is performed in a multicentre setting, higher rates of in-field recurrences and complications were reported [124, 133]. Therefore, nerve-sparing RPLND - if indicated - should be performed by an experienced surgeon in specialised centres.

About 18-30% of patients are found to have retroperitoneal lymph node metastases on RPLND, corresponding to pathological stage II (PS2) disease [133, 134]. If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites [86, 134]. If metastases are present and not treated with adjuvant chemotherapy, recurrence will occur in 31% of patients [134].

The presence of vascular invasion, predominant embryonal carcinoma, pT category as well as a high number of extranodal extension in metastatic nodes may be associated with an increased risk of recurrence in PS2 cases without adjuvant chemotherapy. As yet, the clinical significance of these further parameters remains limited and not applicable in clinical practice [134, 135].

The follow-up after RPLND is simpler and less costly than that carried out during post-orchietomy surveillance because of the reduced need for abdominal CT scans [136]. If there is an indication to perform a staging RPLND, a laparoscopic or robot-assisted RPLND is feasible in expert hands. This minimal-invasive approach cannot be recommended as the standard approach outside of a specialised laparoscopic centre [137].

7.2.2.5 Guidelines for the treatment of stage 1 non-seminomatous germ cell tumour

Recommendations	LE	GR
Inform patients with stage 1 non-seminomatous germ cell tumour (NSGCT) about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection [RPLND]) including treatment-specific recurrence rates as well as acute and long-term side effects.	2a	A*
In patients with stage 1 NSGCT, offer surveillance or risk-adapted treatment based on vascular invasion (see below).	2a	A*
If patients are not willing to undergo surveillance, offer one course of cisplatin, etoposide, bleomycin (BEP) as an adjuvant treatment alternative since it has proven to be superior to RPLND in terms of recurrence rates.	1b	A*
In patients with marker-positive recurrent and/or progressing lesion during surveillance, perform salvage treatment consisting of three or four courses of BEP chemotherapy according to the International Germ Cell Cancer Collaborative Group classification, followed by post-chemotherapy retroperitoneal lymph node dissection if necessary.	2a	A

*Upgraded following panel consensus.

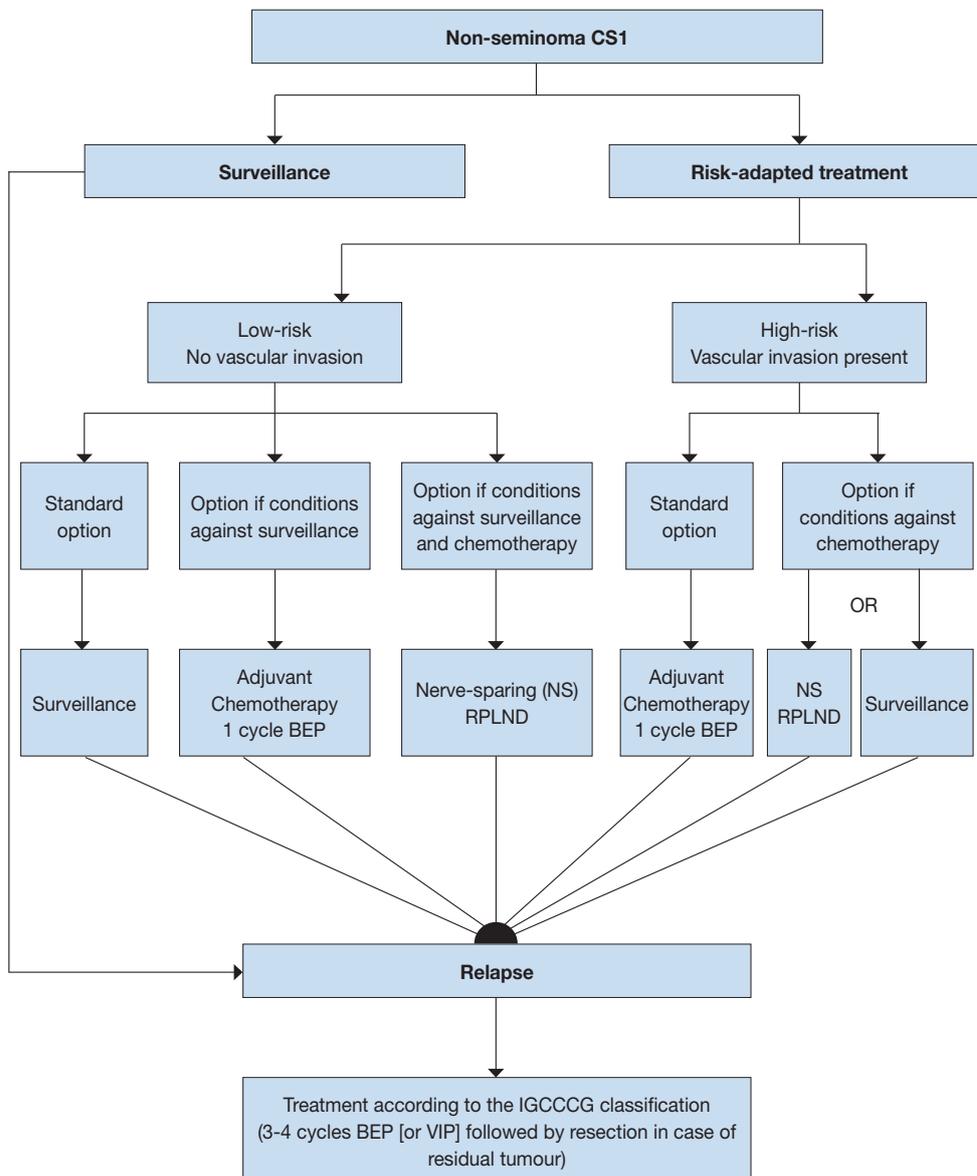
7.2.2.6 Risk-adapted treatment for clinical stage 1 based on vascular invasion

Recommendations	LE	GR
Stage IA (pT1, no vascular invasion): low risk		
Offer surveillance if the patient is willing and able to comply.	2a	A
In low-risk patients not willing (or unsuitable) to undergo surveillance, offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP).	2a	A*
Stage IB (pT2-pT4): high risk		
Offer primary chemotherapy with one course of BEP.	2a	A*
Inform patients having adjuvant chemotherapy about the advantages and disadvantages of one vs. two cycles of BEP.	2a	A*
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.		A*
Offer nerve-sparing retroperitoneal lymph node dissection to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.		A*

*Upgraded following panel consensus.

Figure 1 provides a treatment algorithm for patients with NSGCT stage I.

Figure 1: Risk-adapted treatment in patients with clinical stage 1 non-seminoma NSGCT CS1 [138]*



*All treatment options will need discussing with individual patients, to allow for them to make an informed decision as to their further care.

BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

7.3 Metastatic germ cell tumours

The first-line treatment of metastatic germ cell tumours depends on:

- the histology of the primary tumour;
- prognostic groups as defined by the IGCCCG based on 5,202 non-seminoma and 660 seminoma cases (Table 4.3) [139];
- Marker decline during the first cycle of chemotherapy in “poor prognosis” patients

In relapsed patients a new prognostic score has been developed including response to first-line therapy which can be used to estimate patient outcome following salvage chemotherapy (see below).

7.3.1 CS1S with (persistently) elevated serum tumour markers

Serum tumour markers should be followed closely until levels fall into the reference values according to the expected half-life values for AFP and hCG. The clinical significance of persistently elevated LDH after orchiectomy in stage I disease is unclear. If the marker level for AFP or HCG increases after orchiectomy, the patient has residual disease. An US examination of the contralateral testicle must be performed. In case of NSGCT, if RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum [140]. The treatment of true CS1S NSGT patients is still controversial. They may be treated with chemotherapy and with follow-up as for CS1B patients (high risk, see below) after primary chemotherapy [141], or by RPLND [129].

A population-based study reported on persistently elevated LDH or β -hCG in 19 and 15% of stage I seminoma patients, respectively. These patients frequently had more advanced T stage, but both CSS and OS did not differ from stage I A/B patients independent of treatment [142].

In all patients with germ cell tumours and rising markers, only after orchidectomy, a repeated imaging to detect metastasis is justified in order to individually tailor treatment.

7.3.2 Metastatic disease (stage IIA/B)

7.3.2.1 Stage IIA/B seminoma

Slightly enlarged retroperitoneal lymph nodes < 2 cm in patients without elevated tumour markers offer a diagnostic problem. These lymph nodes may be benign or represent metastases. An observation period of eight weeks with a second staging is recommended unless a biopsy verifies metastatic disease. Treatment should not be initiated unless metastatic disease is unequivocal, (e.g. growth or positive biopsy).

Specific trials (e. g. including RPLND or involved field radiation combined with a single course of carboplatin chemotherapy) are addressing the role of treatment options with potentially lower toxicity as compared to either radiotherapy or chemotherapy with three cycles of BEP.

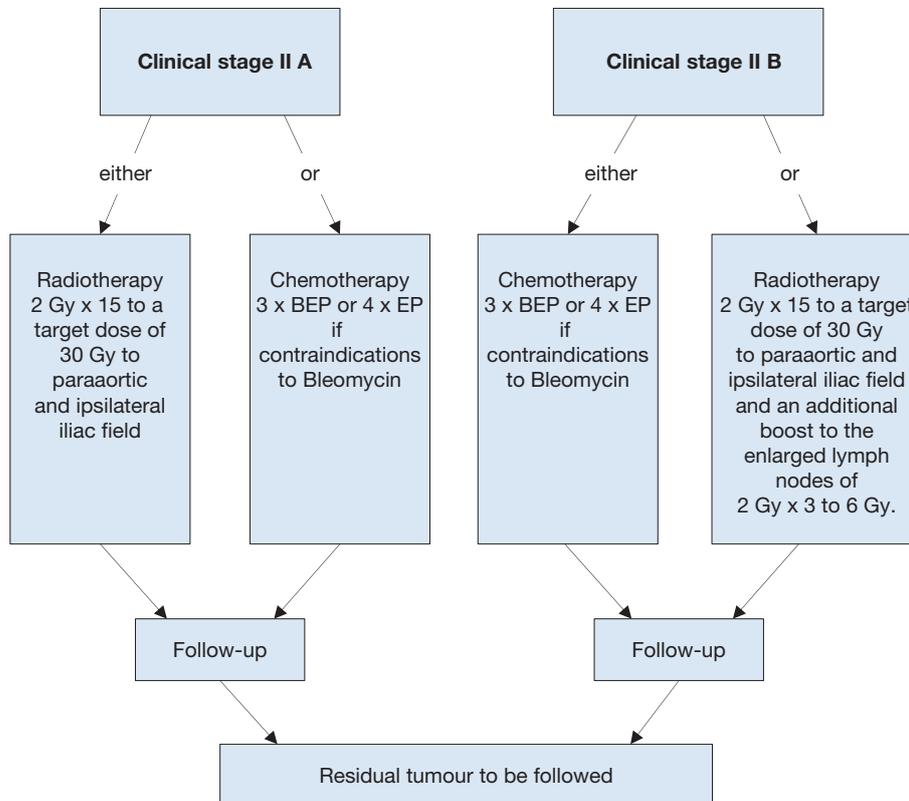
Until recently, the standard treatment for stage IIA/B seminoma has been radiotherapy with reported relapse rates of 9-24% [143, 144]. Accumulating data on long-term morbidity, such as increased risk of cardiovascular events and increased risk of second malignancies following radiotherapy has led to concern. One study displaying a long-term follow-up of 19 years, reports a mortality not due to seminoma seven-fold greater than mortality due to seminoma [145]. Most reports refer to patients irradiated with larger target volumes and higher doses but there are also more recent studies reporting on patients treated with more modern radiotherapy [146]. The radiation dose recommended in stage IIA and IIB is 30 Gy and 36 Gy, respectively. The standard radiation field compared with stage I will be extended from the PA region to the ipsilateral iliac field. In stage IIB, the lateral borders should include the metastatic lymph nodes with a safety margin of 1.0-1.5 cm. This technique yields a relapse-free survival in stage IIA and IIB of 92% and 90%, respectively [143, 144]. Conversely, dose reduction to 27 Gy has been associated with 11% of relapses in stage IIA patients [100, 146].

In patients with stage IIA/B seminoma, chemotherapy with three courses of BEP or four courses of etoposide and cisplatin (EP), in cases with contraindications to bleomycin, is an alternative to radiotherapy. There are no randomised studies comparing radiotherapy vs. chemotherapy. A recent meta-analysis of thirteen high quality studies compared efficacy and toxicity of radiotherapy and chemotherapy in stage IIA and IIB patients [147]. Radiotherapy and chemotherapy appeared to be similarly effective in both stages. Nonetheless a non-significant trend toward a greater efficacy of chemotherapy (HR: 2.17) was shown in stage IIB seminoma. Acute toxicity was almost exclusively reported following chemotherapy, while long-term toxicity was more frequent

following radiotherapy, mainly represented by bowel toxicity and by a higher occurrence of second cancers, almost all occurring in the irradiated field. This may favour the use of chemotherapy, BEP x 3, in stage IIB as standard treatment. In stage IIA, radiotherapy should present the initial treatment option.

Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease [148].

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B



BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

7.3.2.2 Stage IIA/B non-seminoma

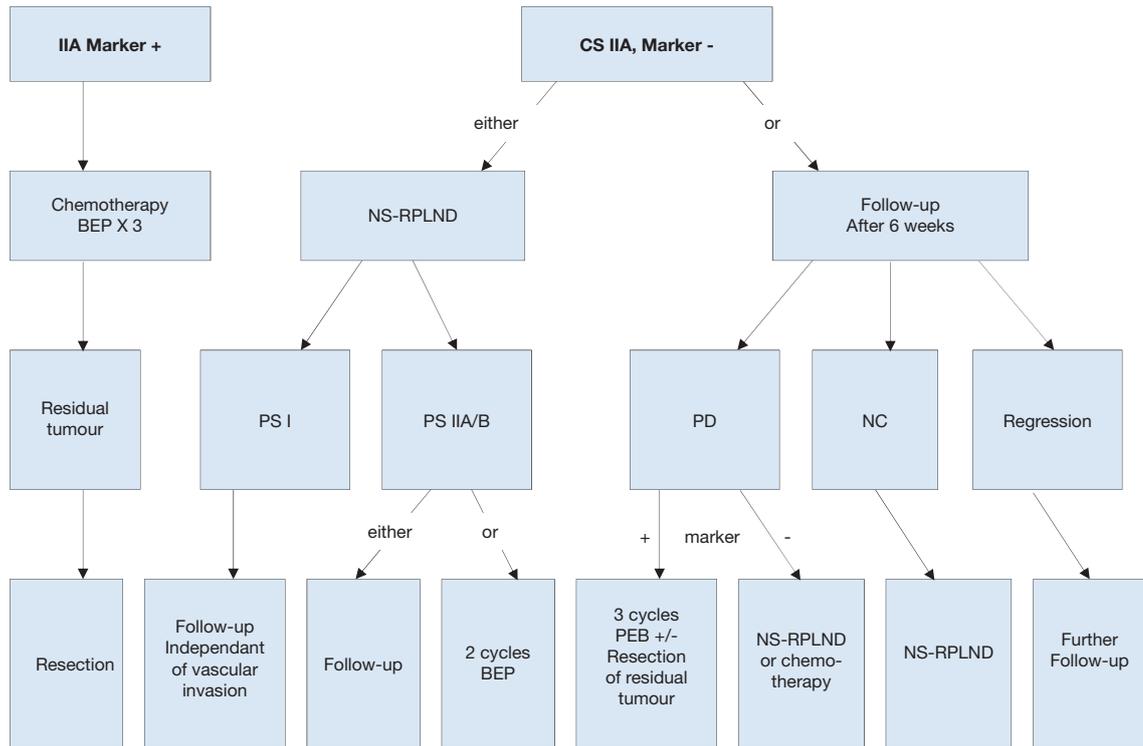
There is a general consensus that treatment should start with initial chemotherapy in all advanced cases of NSGCT except for stage IIA NSGCT disease and pure teratoma without elevated tumour markers, which can be managed by primary RPLND or surveillance to clarify stage [128, 149].

If surveillance is chosen, one follow-up evaluation after six weeks is indicated to document whether the lesion is growing, remaining stable or shrinking. A shrinking lesion is probably non-malignant in origin and should be observed further. A stable or growing lesion indicates either teratoma or an undifferentiated malignant tumour. If the lesion is growing without a corresponding increase in the tumour markers AFP or β -hCG, teratoma is suspected. In such cases “nerve-sparing” RPLND represents the first treatment option and should be performed by an experienced surgeon [149]. Patients with a growing lesion and a concomitant increase in the tumour markers AFP or β -hCG require primary chemotherapy according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations (Figure 2). A CT-or US-guided biopsy, if technically possible, may represent an alternative to surveillance strategy in stage IIA non-seminoma patients. When a marker negative stage IIA/B relapse is diagnosed two or more years following initial diagnosis, a CT-or US-guided biopsy should be advised to confirm the diagnosis of germ cell tumour (GCT) relapse. There is insufficient published data on PET scans in this situation to provide a recommendation on.

Primary chemotherapy and primary ‘nerve-sparing’ RPLND are comparable options in terms of outcome, but early and long-term side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice [150]. The cure rate with either approach will be close to 98% [151-153].

Figure 3 presents the treatment options for patients with NSGCT CS IIA.

Figure 3: Treatment options in patients with non-seminoma clinical stage IIA



BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.

7.3.3 Metastatic disease (stage IIC and III)

7.3.3.1 Primary chemotherapy

7.3.3.1.1 Good prognosis risk group - SGCT

For metastatic seminoma, only very limited data are available from randomised trials and they indicate that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [154]. Recent data indicate that EP x 4 results in cure in almost all cases of good-prognosis seminomatous germ cell cancers [155]. Standard treatment in good-prognosis seminoma should therefore be, BEP x 3 or EP x 4. In the case of contraindications to bleomycin, EP x 4 should be given [156].

Post-chemotherapy masses should be managed as described in Section 7.5.2.

7.3.3.1.2 Intermediate prognosis risk group - seminomatous germ cell tumour

For patients with intermediate-risk seminoma, BEP x 4 or etoposide, cisplatin, ifosfamide (VIP) (in the case of contraindications to bleomycin) are recommended options, although no randomised trial has focused specifically on this group of rare patients [157]. A risk adapted approach with EP x 4 for patients with good prognosis and VIP x 4 for patients with intermediate prognosis metastatic seminoma yielded an OS of 99% and 87% for good and intermediate prognosis patients, respectively [155].

7.3.3.1.3 Good prognosis risk group – non-seminomatous germ cell tumour

For non-seminoma, the primary treatment of choice for metastatic disease in patients with good prognosis risk disease, according to the IGCCCG risk classification, is BEP x 3 (Table 7.1). This regimen was proven superior to cisplatin, vinblastine and bleomycin (PVB) in patients with advanced disease [158, 159]. While data support a three-day regimen of administering combination chemotherapy to be equally effective as a five-day regimen, this is associated with increased toxicity when four cycles are used [160], thus the five-day BEP regimen is recommended.

Table 7.1: cisplatin, etoposide, bleomycin (BEP) regimen (interval 21 days)

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m ²	Days 1-5*
Etoposide	100 mg/m ²	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

*Plus hydration.

In selected cases where bleomycin is contraindicated, EP x 4 can be given [139, 159]. A randomised trial from the French Groupe d'Etude des Tumeurs Genito-Urinaires (GETUG) suggested that when BEP is used in this setting the mortality rate was half that of EP, although the difference did not reach statistical significance [161]. Furthermore, the incidence of active cancer in the retroperitoneal specimen at post-chemotherapy retroperitoneal lymph node dissection was, however, to significantly higher in patients who received EP x 4 as compared to BEP x 3 (31.9% vs. 7.8%, $p < 0.001$) [162, 163]. The risk of requiring post-RPLND adjuvant chemotherapy could be higher after EP x 4 which could thereby offset a hoped-for less toxic treatment.

Higher age is an adverse factor for the efficacy of BEP x 3 [164].

Therapy should be given without reduction of the doses at 21-day intervals; delaying the following chemotherapy cycle is justified only in cases of fever with granulocytopenia $< 1,000/\text{mm}^3$ or thrombocytopenia $< 100,000/\text{IU}$. Neutropenia without fever is not by itself a reason to delay the next cycle. There is no indication for prophylactic application of haematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF). However, if infectious complications have occurred during chemotherapy or the treatment interval was delayed due to myelotoxicity, prophylactic administration of G-CSF is recommended for the following cycles [165].

7.3.3.1.4 Intermediate prognosis risk group – non-seminomatous germ cell tumour

The 'intermediate prognosis' group in the IGCCCG has been defined as patients with a five-year survival rate of about 80%. The available data support BEP x 4 as standard treatment [139, 166]. A randomised trial compared BEP x 4 to BEP x 4 with the addition of paclitaxel (T-BEP) with no significant improvement in OS [167]. The overall toxicity with T-BEP was higher than with BEP, therefore it cannot be recommended as a standard approach.

7.3.3.1.5 Poor prognosis risk group - NSGCT

For patients with a 'poor prognosis' non-seminoma as defined by the IGCCCG, standard treatment consists of BEP x 4. Four cycles of cisplatin, etoposide and ifosfamide (PEI) have the same effect, but are more myelotoxic [168, 169]. The five-year PFS is between 45% and 50%. Four randomised trials have shown no advantage in OS for high-dose chemotherapy in the overall 'poor prognosis' patients group [33, 170-172]. However, patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [33, 34]. An online calculator is available at www.igr.fr/calculation-tumor/NSGCT.xls. Recently, an international randomised phase III trial (GETUG 13) conducted in 263 patients with IGCCCG poor-risk NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS, but not OS in patients with an early unfavourable tumour marker decline [35]. Based on the results from this trial, patients with an unfavourable tumour marker decline after BEP x 1 should be switched to a more intensive chemotherapy regimen [173, 174]. Further prospective trials/registries are planned to validate this approach.

Additional patient groups that may benefit from up-front dose intensification are those with mediastinal primary non-seminoma and patients with brain metastases at initial diagnosis [175, 176].

Since a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [34, 177], poor prognosis patients should still be treated in ongoing prospective trials or registries, whenever possible. Patients meeting 'poor-prognosis' criteria should be transferred to a reference centre as a better outcome was reported for intermediate and poor prognosis patients who had been treated within a clinical trial in a high volume centre [12, 155]. There are no general recommendations for treatment modifications for patients with a poor general condition (Karnofsky $< 50\%$) or extended liver infiltration ($> 50\%$), but two small reports indicate that a first cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcome. However, the number of subsequent cycles of full-dose therapy should not be reduced after a first low-dose induction cycle [178, 179].

Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome: adapting the doses of the BEP regimen in the first cycle of chemotherapy (only three days of EP without bleomycin) was suggested to reduce the risk of early death in this setting [178].

7.4 Restaging and further treatment

7.4.1 Restaging

Restaging is performed by imaging investigations and re-evaluation of tumour markers. Upon marker decline and stable or regressive tumour manifestation, chemotherapy will be completed (three or four cycles, depending on the initial stage) [139, 180, 181]. In the case of marker decline, but growing metastases, resection of the tumour is obligatory after termination of induction therapy, other than in an emergency, according to local tumour growth [182].

Patients with clear upfront progression (primary cisplatin refractory) should be switched to experimental new drug trials [183]. Patients with slow marker decline after the first one-two cycles of chemotherapy are candidates for dose intensification (see Section 7.4.3.1.5.). Patients with a low-level hCG marker plateau post-treatment should be observed to see whether complete normalisation occurs. In patients with a low plateau serum AFP level after chemotherapy, surgery of residual masses should be performed, with post-surgery AFP monitoring. Salvage chemotherapy is indicated for documented marker rise only [184, 185].

7.4.2 Residual tumour resection

7.4.2.1 Seminoma

A residual mass of seminoma should not be primarily resected, irrespective of the size, but controlled by imaging investigations and tumour markers [186-189].

Fluorodeoxyglucose-positron emission tomography has a high negative predictive value in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled > 2 months after chemotherapy. In patients with residuals of > 3 cm, FDG-PET should be performed in order to gain more information on the viability of these residuals. In patients with residuals of < 3 cm, the use of FDG-PET is optional [45].

In the case of a post-chemotherapy mass that is still positive at reclassification FDG-PET with no volume increase, a second FDG-PET should be performed six weeks later. Alternatively, a biopsy should be taken to ascertain persistent disease. In these cases as well as in those with progressive disease (i.e. a growing mass which up-takes contrast medium at CT scans or radionuclide tracer at FDG-PET), salvage therapy is indicated (usually chemotherapy or radiotherapy) [190-192]. Patients with persistent and progressing hCG elevation after first line chemotherapy should immediately proceed with salvage chemotherapy. Progressing patients without hCG progression should undergo histological verification (e. g. by biopsy or mini-invasive or open surgery) before salvage chemotherapy is given.

When RPLND is indicated, this should be performed in referral centres, as residuals from seminoma may be difficult to remove due to intense fibrosis [191]. Ejaculation may be preserved in these cases [193].

7.4.2.2 Non-seminoma

Following first-line BEP chemotherapy, only 6-10% of residual masses contain viable cancer, 50% contain mature teratoma, and 40% contain necrotic-fibrotic tissue [194]. FDG-PET is not indicated to re-stage patients after chemotherapy [47]. In cases of complete remission after first line chemotherapy (no visible tumour), tumour resection is not indicated [195, 196]. Residual tumour resection is mandatory in all patients with a residual mass > 1 cm in the short axis at cross-sectional CT imaging [197-200].

The role of surgery is debated in patients with retroperitoneal residual lesions < 1 cm. There is still a risk of residual cancer or teratoma although the vast majority of patients (> 70%) harbour fibro-necrotic tissue [201]. Proponents of post-chemotherapy-RPLND for all patients refer to the fact that both teratoma and vital malignant germ cell tumours are still found after radiologic complete remission in lesions < 10 mm [202]. The alternative is to put patients with residual disease < 1 cm on an observation protocol based on recurrence data of 6-9% depending on the time of follow-up [195, 196]. In the series with a longer observation of 15.5 years, 12 of 141 patients (9%) relapsed after having achieved a complete response after primary treatment [196], but eight of the 12 relapsing patients were cured. Therefore, patients treated with first-line chemotherapy should be informed about this life-long risk of recurrence in the order of 10% before consenting to observe residual lesions < 1 cm. Patients after salvage chemotherapy or high-dose chemotherapy in first or subsequent salvage situations harbour vital tumour at a much higher rate [203]. Therefore, there is an indication to perform surgery in salvage patients even with residual disease < 1 cm [195, 196].

If residual surgery is indicated, all areas of primary metastatic sites must be completely resected within two-six weeks of completion of chemotherapy. If technically feasible, a bilateral nerve-sparing procedure should be performed. There is growing evidence that template resections with unilateral preservation of nerves in selected patients yield equivalent long-term results compared to bilateral systematic resections in all patients. The mere resection of the residual tumour (so called lumpectomy) should not be performed [196, 201, 204-207].

In persistent larger volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within two-six weeks of completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed [196, 201, 204]. Laparoscopic RPLND may yield similar outcomes to the open procedure in very selected cases of very low residual disease and in very experienced hands, but it is not recommended outside a specialised laparoscopic centre [208-210].

7.4.3 **Timing of surgery in the case of multiple sites**

In general, residual surgery should start at the location with the highest volume of residual disease. The histology may diverge in different organ sites [197]. In cases of retroperitoneal and lung residual masses, the presence of fibro-necrotic tissue in the retroperitoneum is associated with a probability as high as 90% that lung masses contain the same histology [211].

Resection of contralateral pulmonary lesions is not mandatory in cases where pathologic examination of the lesions from the first lung show complete necrosis. However, discordant histology between both lungs may occur in up to 20% of patients [212, 213].

7.4.3.1 *Quality and intensity of surgery*

Post-chemotherapy surgery is always demanding. Most of the time, post-chemo RPLND does not require further interventions on abdominal or retroperitoneal organs. About a third of patients may require a planned intervention where removal of organs affected by the disease (for example kidney, psoas muscle or gross vessels) is performed and followed by *ad hoc* reconstructive surgery (e.g. vascular interventions such as vena cava or aortic prostheses) [214, 215]. In patients with intermediate- or poor-risk and residual disease > 5 cm the probability of vascular procedures is as high as 20% [216]. This surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Even with centralisation of treatment the median number of RPLNDs performed per surgeon/year in the U.K. is six [217]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6% to 0.8% [13]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [14].

7.4.3.2 *Salvage and desperation surgery.*

Surgery of resectable disease after salvage treatment remains a potentially curative option in all patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy was improved, 70% at 10 years, following taxane-containing regimens [218]. Also, in the case of extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [219, 220].

Desperation surgery refers to resection of non-responsive or progressive (e.g. rising markers) disease following salvage chemotherapy. When the disease is resectable, a significant proportion of these patients can be rendered disease-free in the long term [221].

7.4.3.3 *Consolidation chemotherapy after secondary surgery*

After resection of necrosis or mature/immature teratoma, no further treatment is required. In cases of incomplete resection of viable cancer, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e.g. 'poor prognosis' patients) [205] (caution: cumulative doses of bleomycin). After complete resection of 'vital' tumour < 10% of the total volume, especially in patients in an initially good prognosis group according to IGCCCG, the relapse rate is very low and adjuvant chemotherapy is not beneficial for preventing further relapse [222]. The prognosis will definitely deteriorate if vital malignant neoplasm is found in resection specimens after second- and third-line chemotherapy. In this latter situation, post-operative chemotherapy is not indicated and is unable to improve the prognosis [223].

7.4.4 **Systemic salvage treatment for relapse or refractory disease**

Cisplatin-based combination salvage chemotherapy will result in long-term remissions in about 50% of the patients who relapse after first-line chemotherapy, but the results are highly dependent on several prognostic factors [224]. The regimens of choice are four cycles of a triplet regimen including cisplatin and ifosfamide plus a third agent: etoposide (PEI/VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 7.2) [225]. No randomised trial has compared these regimens. Due to their potentially lethal risk of haematological toxicity, these regimens should be used with G-CSF support and by well-trained oncologists.

The only available randomised trial comparing standard-dose vs. high-dose chemotherapy plus transplant in the salvage setting showed no benefit in OS in patients treated with three cycles of vinblastine, ifosfamide, and cisplatin (VeIP) plus one cycle of consolidation high-dose chemotherapy, compared with VeIP x 4 [226]. Due to several methodological reasons this trial design can no longer be considered state of the art.

There is clear evidence from large retrospective analyses that there are different prognostic groups in the case of relapse after first-line chemotherapy [227, 228], and the Lorch-Beyer score has resulted in five prognostic subgroups (Table 7.3). Several recent trials have confirmed this score [229, 230]. As in first-line therapy, the prognostic impact of tumour marker decline has also been demonstrated in the salvage setting [231]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [232].

A second large analysis in this cohort of 1,600 patients showed an improvement of about 10-15% in OS in patients from all prognostic subgroups when treated with high-dose salvage therapy compared to standard dose therapy. To prospectively confirm this finding, an international randomised trial of high-dose vs. conventional dose chemotherapy in patients with first-line relapse has started (Tiger trial). If high-dose chemotherapy is used as a salvage treatment, sequential treatment cycles of high-dose carboplatin and etoposide HD-CE should be preferred to a single high-dose regimen because the former is associated with less toxicity-related deaths [233].

It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at experienced centres.

Table 7.2: Standard PEI/VIP, TIP and GIP chemotherapy (interval 21 days)

Regimen	Chemotherapy agents	Dosage	Duration of cycles
PEI/VIP	Cisplatin*	20 mg/m ²	Days 1-5
	Etoposide	75-100 mg/m ²	Days 1-5
	Ifosfamide†	1.2 g/m ²	Days 1-5
TIP	Paclitaxel	250 mg/m ² xx	24 hour continuous infusion day 1
	Ifosfamide†	1.5 g/m ²	Days 2-5
	Cisplatin*	25 mg/m ²	Days 2-5
	Alternative schedule		
GIP	Paclitaxel	175 mg/m ²	Day 1, 3 hour infusion
	Ifosfamide†	1.2 g/m ²	Days 1-5
	Cisplatin*	20 mg/m ²	Days 1-5
GIP	Gemcitabine	1000 mg/m ²	Day 1 + 5
	Ifosfamide	1200 mg/m ²	Days 1-5
	Cisplatin	20 mg/m ²	Days 1-5

* Plus hydration.

† Plus mesna protection.

xx An MRC schedule uses paclitaxel at 175 mg/m² in a 3 hour infusion [234].

The International Prognostic Factors Study Group score, comprised of seven important factors, is listed in Table 7.3. Using these factors, 5 risk groups (very low risk = -1 points; low risk = 0 points; intermediate-risk = 1-2 points, high risk = 3-4 points; and very high risk > 5 points) were identified with significant differences in PFS and OS. Table 4.3 illustrates the five risk groups and the corresponding two-year PFS and three-year OS rates [235].

Table 7.3: The International Prognostic Factors Study Group Score Construction [228]

Points	-1	0	1	2	3
Variable					
Histology	Seminoma	Non-seminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
Response		CR/PRm-	PRm+/SD	PD	
PFI		> 3 months	≤ 3 months		
AFP salvage		Normal	< 1000	1000	
hCG salvage		< 1000	1000		
LBB		No	Yes		

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LBB = liver, bone, brain metastases; PD = progressive disease; PFI = progression-free interval.

Table 7.4: PFS and OS estimates for all patients according to IGCCCG-2 prognostic score [228]

	N	%	HR	2-years PFS	3-year OS
Score (n = 1,435)					
Very Low	76	5.30	1	75.1	77.0
Low	257	17.9	2.07	52.6	69.0
Intermediate	646	45.0	2.88	42.8	57.3
High	351	24.5	4.81	26.4	31.7
Very High	105	7.3	8.95	11.5	14.7
Missing	159				

7.4.5 **Second relapse**

There are no randomised trials for patients with second relapse; however, conventional therapy does not appear to be very effective. For patients having received two series of conventionally dosed therapy (first-line and first salvage), High-dose (HD) chemotherapy with autologous stem cell support should be used [228]. Even with HD-therapy the chance of cure is only 20-25%.

Refractory disease: Patients relapsing within four-eight weeks after platinum-based therapy or who are progressing despite platinum-based therapy as well as those relapsing shortly after HD chemotherapy are considered cisplatin refractory. For those patients, combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45%. Targeted agents have mostly failed [236-238]. Cisplatin re-challenge in association with gemcitabine and paclitaxel, could be considered in patients with good renal function [239].

Patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15-20% chance of long-term cure [219, 240]. Immunotherapy with PD1- checkpoint inhibitors is currently studied due a substantial expression of PDL1 in germ cell tumours, in most series about 50% of tumour cells or tumour infiltration cells express PDL1.

7.4.5.1 *Late relapse (> two years after end of first-line treatment)*

Late relapse is defined as recurrence more than two years following cure after chemotherapy for metastatic TC, with, or without, residual tumour surgery and occurs, according to a pooled analysis, in 1.4% and 3.2% in seminoma and non-seminoma patients, respectively [241, 242]. If feasible, all lesions of late relapsing non-seminoma patients should be removed by radical surgery.

Patients with rapidly rising hCG may benefit from induction salvage chemotherapy before complete resection, but in most patients surgery should be performed irrespective of the level of their tumour markers in order to completely resect all undifferentiated germ-cell tumour, mature teratoma with or without somatic transformation [204, 243, 244].

Survival strongly depends on the histology of the removed lesions rather than on the initial germ cell cancer. Interestingly, in a population-based study all late-relapsing seminoma patients had viable germ cell tumour, whereas teratoma or necrosis was found in half of the patients with initial non-seminoma [245].

If the lesions are not completely resectable, biopsies should be obtained for histological assessment, and salvage chemotherapy should be initiated according to the histological results. In these cases, consultation of an experienced pathologist is required to avoid misinterpretation of the therapeutic morphological changes in the germ cell neoplasms [246]. If the patient responds to salvage chemotherapy, secondary surgery should be conducted whenever possible. In the case of unresectable, but localised, refractory disease, stereotactic or conventional radiotherapy may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [247].

7.4.5.2 *Treatment of brain metastases*

Brain metastases occur in the frame of the initial diagnosis of metastatic disease or a systemic relapse and rarely as an isolated relapse. The long-term survival of patients presenting with brain metastases at initial diagnosis is poor (30-50%), but it is even poorer when brain metastasis develops as recurrent disease (the five-year survival-rate is 2-5%) [248, 249]. A large international database comprising 523 patients reported 48% three-year OS rates in patients with brain metastases at initial diagnoses and 27% three-year OS rates for patients with brain metastases at relapse [250]. Chemotherapy was the initial treatment in this case, which proved particularly effective in a first line setting (potentially even as dose-intensified therapy upfront) while data support the use of multimodal treatment particularly in relapsed patients [250]. Consolidation radiotherapy, even in the case of a total response after chemotherapy should thus be used in patient with brain metastases

at relapse, but this option must be carefully discussed in a first-line setting [251]. Surgery can be considered in the case of a persistent solitary metastasis, depending on the systemic state, the histology of the primary tumour and the location of the metastasis.

7.4.6 Guidelines for the treatment of metastatic germ cell tumours

Recommendations	LE	GR
Treat low volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like 'good or intermediate prognosis' advanced NSGCT, with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	2	A
In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either retroperitoneal lymph node dissection (RPLND) or biopsy. If not possible, repeat staging after six weeks of surveillance before making a final decision on further treatment.	3	B
In metastatic NSGCT with an intermediate prognosis, treat with four courses of standard BEP.	1	A
In metastatic NSGCT with a poor prognosis, treat with one cycle of BEP, followed by tumour marker assessment after three weeks: in the case of an unfavourable decline, initiate chemotherapy intensification. In the case of a favourable decline, continue BEP up to a total of four cycles.	1	A
Perform surgical resection of residual masses after chemotherapy in NSGCT in the case of visible residual masses and when serum levels of tumour markers are normal or normalising.	2	A
Initially offer radiotherapy for seminoma CS IIA. When necessary, use chemotherapy as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.	2	B
Initially offer chemotherapy in seminoma stage CS IIB (BEP x 3 or etoposide, cisplatin x 4, in good prognosis) as an alternative to radiotherapy.	1a	A
Treat seminoma stage IIC and higher, with primary chemotherapy according to the same principles used for NSGCT.	1	A

8. FOLLOW UP AFTER CURATIVE THERAPY

8.1 Rationale for follow-up

The primary aim of follow-up in the first five years is the timely diagnosis of recurrent disease in order to be able to treat the patient with curative intent with the least aggressive therapy [241]. An adequate follow-up relies on the profound knowledge about TC with regards to histology, stage, primary treatment and treatment success. Follow-up has to be tailored to each individual patient and the schedule has to be acceptable to the patient, the physician, as well as the health care system. The interval of follow-up visits and the clinical investigations to be performed at each visit should depend on the risk of relapse, in general, and on the likely site of relapse in an individual patient [252]. Only one RCT was published addressing the implication of different follow-up schedules and the use of imaging and tumour markers [129]. Several recent publications have added valuable information and recommendations [84, 96, 97, 101, 103, 126, 253-255], contributing to the development of consensus recommendations and by the European Society for Medical Oncology Testicular Cancer Consensus Committee [256].

In recognition of the ionizing radiation exposure risks associated with repeated CT scanning [257] a reduction in the number of follow up CT scans advised has been seen in these past years [1, 258].

Looking at the different risks of relapse depending on diagnosis and initial treatment three major follow-up groups can be defined:

1. patients with seminoma stage I;
2. patients with non-seminoma stage I on active surveillance;
3. all patients having received either adjuvant treatment or curative chemotherapy for good- and intermediate-prognosis metastatic disease (according to the IGCCCG) achieving a complete remission with, or without, surgery (for seminoma this includes residual lesions < 3 cm, or residual lesions > 3 cm that are PET-negative).

It is important to note that patients not achieving a complete remission or presenting with poor prognosis disease should be followed up individually in specialised centres.

Tables 8.1-8.3 show the minimal recommendations for follow up of the three different groups based on recommendations developed at a consensus conference [256].

Generally, MRI of the abdomen can be used instead of CT in experienced centres. Regarding the use of US of the contralateral testis, the majority of the consensus meeting participants voted against repeat US investigation, both in case of negative biopsy (21/31) and also if no contralateral biopsy has been performed (17/32).

Follow up for relapse beyond five years is generally not recommended. A very late relapse (VLR) after five years is a rare event occurring in approximately 0.5% of patients according to a population-based analysis [245]. The aim of follow up beyond five years therefore shifts to detection of late side effects of treatment.

Most patients with VLR are diagnosed due to symptoms, however in up to 50% elevated tumour markers can be found in both seminomatous and non-seminomatous germ cell tumours [245, 259]. Patient education about relapse symptoms and physician awareness is a very important part of survivorship management. The early use of imaging and tumour markers in case of suspicion of relapse is encouraged.

Table 8.1: Recommended minimal follow-up for seminoma stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic computed tomography/magnetic resonance imaging	2 times	2 times	Once at 36 months	Once at 60 months	

Table 8.2: Recommended minimal follow-up for non-seminoma stage I on active surveillance

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times**	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
Abdominopelvic computed tomography/magnetic resonance imaging	2 times	At 24 months***	Once at 36 months*	Once at 60 months*	

* Recommended by 50% of the consensus group members.

**In case of high risk (LVI+) a minority of the consensus group members recommended six times.

***In case of high risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.

Table 8.3: Recommended minimal follow up after adjuvant treatment or complete remission for advanced disease (excluded: poor prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	*	*	*	*	

*Same time points as abdominopelvic CT/MRI in case of pulmonary metastases at diagnosis.

**In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.

8.2 Quality of life and long-term toxicities after cure of testicular cancer

The vast majority of patients will be cured and five-year relative survival rates approximate 95% in Western Europe. Furthermore, TC patients are usually between 18 and 40 years at diagnosis such that life expectancy after cure extends over several decades [260]. Patients should be informed before treatment of common long-term toxicities, which are probably best avoided by adherence to international guidelines. Treatment of stage I TC is controversial with some experts advocating surveillance for all, thereby avoiding unnecessary adjuvant chemotherapy [118], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with its known long-term toxicities as quite appealing [261]. Unfortunately, it is not known which treatment spares most patients long-term toxicities, which so far seem to be absent or mild after adjuvant chemotherapy [120, 127, 262].

During follow-up, patients should be screened and treated for known risk factors such as high blood pressure, hyperlipidaemia and testosterone deficiency. When follow-up by the TC expert is discontinued, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up might be helpful [241, 263]. The following overview is not complete and interested readers are referred to review articles on this topic [260, 263, 264].

8.2.1 Second malignant neoplasms (SMN)

Treatment-induced SMN usually occur after the first ten years [263]. The risk for solid SMN increases with younger age at radio- or chemotherapy and remains significantly elevated for at least 35 years [110, 265-267]. Radiotherapy-related SMN are primarily localised within or close to the RT field (colon, stomach, pancreas, bladder and the urinary tract) [110, 111, 266-269]. Hauptmann *et al.* could demonstrate a remarkably clear radiation-dose relationship to gastric- and pancreatic cancer [175, 250]. Fung *et al.* demonstrated that modern cisplatin-based chemotherapy was associated with a 40% increased risk of a solid SMN [270].

8.2.2 Leukaemia

In a series of 40,576 TC survivors, the observed/expected ratio for developing a leukaemia, mostly acute myeloid (AML) and lymphoblastic leukaemia was 2.6 [271]. The risk of AML seems to be both related to the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m² have been shown to increase the subsequent risk of AML [272]. It is important to keep in mind that the majority of TC patients do receive much lower doses of etoposide such that the absolute risk of AML after three to four courses of BEP is very low, and in patients requiring high-dose chemotherapy with cumulative etoposide doses exceeding this threshold, less than 1.5% have been reported to suffer from AML. There is a cumulative dose-disease relationship regarding cisplatin and AML. Chemotherapy-induced leukaemia is usually diagnosed within the first ten years after treatment for TC and has a very poor prognosis [273].

8.2.3 Infections

Chemotherapy-treated TC survivors (TCSs) have a higher risk of dying from infections than the normal population, (SMR 2.48, 95% CI: 1.70 to 3.50) [274]. This is possibly due to long-term depression of the bone-marrow, but also complications of subsequent salvage treatment (which was not reliably registered) or extensive or subsequent surgical treatment might lie behind these numbers. Furthermore, asymptomatic pulmonary fibrosis by mediastinal radiotherapy and/or bleomycin may render TCSs vulnerable to potentially deadly pneumonias many years after treatment.

8.2.4 **Pulmonary complications**

Chemotherapy exposed TCSs have a nearly three-fold increased risk of dying of pulmonary diseases than the normal population [274]. Bleomycin-induced lung toxicity may affect 7% to 21% of patients in the long term, resulting in death in 1%-3% [275]. TCSs treated with high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured by surgery only [276]. Intriguingly, long-term pulmonary complications were associated with the cumulative cisplatin dose and not to the dose of bleomycin [276]. Pulmonary function recovered during repeated assessments over five years in almost all other assessed 565 TCSs [277]. Of note, an association with risk factors such as reduced renal function, age, tobacco-smoking, and cumulative chemotherapy, were not associated with pulmonary function, but with pulmonary embolism, lung surgery, and poor IGCCCG risk group [277].

8.2.5 **Cardiovascular toxicity**

Thromboembolic events (mostly venous) occur more frequently in patients with GCT receiving chemotherapy than in other young male adults treated with chemotherapy for other cancers [278]. Low-dose heparins used during the course of chemotherapy may prevent the onset of thromboembolic events [279], though level 1 evidence is lacking. Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population [274, 280]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [123, 281]. A recent report estimated even a 0.24% incidence of major vascular events during cisplatin-based chemotherapy [278]. The metabolic syndrome is a strong predictor for CVD and its components, hypertension, obesity and hypercholesterolemia, increase with treatment intensity [282, 283]. Circulating residual serum platinum might exert endothelial stress and thereby possibly lead to hypertension [284],[285]. Furthermore, exposure to circulating platinum has been shown to be associated with paraesthesia, hypogonadism, and hypercholesterolaemia [285].

8.2.6 **Raynaud-like phenomena**

Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually ascribed to the application of bleomycin [286, 287]. Cisplatin is believed to contribute to cold-induced vasospasms. Vogelzang *et al.* reported that the incidence of Raynaud's phenomenon was higher after treatment with CVB than after vinblastine and bleomycin only, 41% vs. 21%, respectively [288].

8.2.7 **Neurotoxicity**

Cisplatin induces a symmetric dose-dependent sensory, distal, length-dependent glove and stocking paraesthesias, affecting 29% of TCSs who received cisplatin-based chemotherapy as opposed to 10% after orchiectomy alone [289]. Application of five or more cycles increases the frequency of this symptom to 46%. Paclitaxel-induced acute neuropathy consists of an acute pain syndrome, which usually develops within three days of paclitaxel administration, or within a week. Platinum is measurable in the serum of TCSs many years after its application and the intensity of paraesthesias is more strongly associated with platinum serum level than with the cumulative dose of applied cisplatin [284].

8.2.8 **Ototoxicity**

Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly frequencies of 4,000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [290-292]. Both hearing impairment and tinnitus are considerably increased after application of 50 mg/m² cisplatin over two days as compared to 20 mg/m² over five days (odds ratio 5.1 and 7.3, respectively), indicating a higher impact of serum peak concentrations than cumulative doses [289]. A significant association between glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [293, 294]. Hopefully, increasing insight into the pathogenesis of and vulnerability for this complication will lead to more individualised treatment in the future.

8.2.9 **Nephrotoxicity**

Cisplatin-based chemotherapy may lead to long-term renal function impairment in 20-30% of TCSs [289-292]. In TC patients, reduced renal elimination of cisplatin and bleomycin might increase the risk of other toxicities, e.g. bleomycin-related pneumonitis [295, 296]. However, a comprehensive assessment of 1,206 Danish TCSs did not reveal a significant association between chemotherapy-induced impaired renal function and other toxicities [279]. Renal recovery was poor after 5 or more cycles of BEP as compared to after BEP x3 [279].

8.2.10 **Hypogonadism**

Testicular endocrine dysfunction comprises insufficient testosterone production and/or compensatory increased Luteinizing hormone (LH) levels. Subnormal testosterone levels have been reported in TCSs treated with chemotherapy, when compared to those treated with surgery only or the general population [262, 297].

8.2.11 **Fatigue**

Chronic fatigue (CF) is described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest, and persists for more than six months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [298]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs at a median of twelve years after treatment for TC when compared with the age-matched Norwegian population (10%) [299]. Of note, the prevalence of CF increased from 15% to 27% during a 10 year period in long-term TCSs [300].

8.2.12 **Quality of life**

Quality of life (QoL) is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social and physical functions [299]. When comparing three or four cycles of BEP in good risk patients, all outcomes favour treatment with three courses [160]. After one and two years, one third of patients reported an improvement in global QoL after chemotherapy, while one fifth of patients reported deterioration, with no difference between treatment groups. In adjuvant treatment of non-seminoma stage I patients, there was no difference in short-term or long-term (5 year) QoL between RPLND or one course of BEP [301]

9. TESTICULAR STROMAL TUMOURS

9.1 **Classification**

Non-germ-cell tumours of the testicle include sex cord/gonadal stromal tumours and miscellaneous nonspecific stromal tumours. The different histological subtypes of testicular tumours are defined according to the WHO classification 2016 (adapted) [30].

9.1.1 **Epidemiology and prognosis**

Sex cord stromal tumours comprise less than 5% of testicular neoplasms. Data from the National Cancer Data Base, published in 2016, showed that 0.39% of patients (315/79,120) were diagnosed with primary malignant Leydig or Sertoli cell tumours [113]. Of these 315 patients 250 (79%) had malignant Leydig cell tumours and 65 (21%) had malignant Sertoli cell tumours. Overall survival at one and five years for CS Leydig cell tumours was 98% (95% CI: 96-100) and 91% (95% CI: 85-96), respectively, and for CSI Sertoli cell tumours OS was 93% (95% CI: 83-100) and 77% (95% CI: 62-95), respectively ($p = 0.015$).

Conclusion is that five-year survival estimates of stage I Leydig and Sertoli cell tumours are significantly lower compared to those of stage I germ cell tumours with Sertoli cell tumours significantly worse than Leydig cell tumours.

A recent systematic review [285] analysing the impact of previously identified pathologic risk factors on harbouring occult metastatic disease (OMD) in patients with CS I testicular stromal tumours showed an increased risk of occult metastatic disease for each additional risk factor ($P < .001$). Five-year occult metastatic disease-free survival was 98.1% for those with < 2 risk factors vs. 44.9% for those with ≥ 2 risk factors ($P < .001$). Whilst the existing literature does not support making firm recommendations, it seems to be of interest to risk-stratify patients for future research and initiate adjuvant therapy in higher-risk patients.

These data support the importance of large databases to evaluate the efficacy of treatment in rare neoplasms.

9.2 **Leydig cell tumours**

9.2.1 **Epidemiology**

Leydig cell tumours constitute about 1-3% of adult testicular tumours [302, 303] and 3% of testicular tumours in infants and children [303]. These tumours are most common in the third to sixth decade in adults, with a similar incidence observed in each decade. Another peak incidence is seen in children aged between three and nine years. Only 3% of Leydig cell tumours are bilateral [302]. These tumours occur in about 8% of patients with Klinefelter's syndrome [303].

9.2.2 **Pathology of Leydig cell tumours**

Leydig cell tumours are the most common type of sex cord/gonadal stromal tumours. Histopathologically, they are well delineated and usually up to 5 cm in diameter. They are solid, yellow to tan in colour, with haemorrhage and/or necrosis in 30% of cases. Microscopically, the cells are polygonal, with eosinophilic cytoplasm and occasional Reinke crystals, regular nucleus, solid arrangement and capillary stroma. The cells express vimentin, inhibin, protein S-100, steroid hormones, calretinin and cytokeratin (focally) [64].

Approximately 10% of Leydig cell tumours are malignant and present with the following parameters [304, 305]:

- large size (> 5 cm);
- older age;
- increased mitotic activity (> 3 per 10 high-power field [HPF]);
- vascular invasion;
- cytological atypia;
- increased MIB-1 expression;
- necrosis;
- infiltrative margins;
- extension beyond the testicular parenchyma;
- DNA aneuploidy.

9.2.3 **Diagnosis**

Patients either present with a painless enlarged testis or the tumour is found incidentally on US. In up to 80% of cases, hormonal disorders with high oestrogen and oestradiol levels, low testosterone, and increased levels of LH and FSH are reported [306, 307], while negative results are always obtained for the testicular germ cell tumour-markers AFP, hCG, LDH and PLAP. Up to 10% of adult patients present with gynaecomastia [307, 308].

Diagnostic work-up must include markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes, and CT of chest and abdomen. On US, it may be possible to observe well-defined, small, hypoechoic lesions with hypervascularisation, however, the appearance is variable and is indistinguishable from germ-cell tumours [309]. Contrast-enhanced US [310] or contrast-enhanced MRI [311] may improve the diagnosis. The proportion of metastatic tumours in all published case reports is less than 10%. In three old series with long follow-up, eighteen metastatic tumours were found in a total of 83 cases (21.7%) [302, 304, 312], while 5 recently published studies with long follow-up reported only 2 metastatic tumours in 156 patients (1.3%) [113, 307, 308, 313, 314].

9.3 **Sertoli cell tumours**

9.3.1 **Epidemiology**

Sertoli cell tumours account for fewer than 1% of testicular tumours, and the mean age at diagnosis is around 45 years, with sporadic cases under 20 years of age [315, 316]. On rare occasions, these tumours may develop in patients with androgen insensitivity syndrome and Peutz-Jeghers syndrome.

9.3.2 **Pathology of Sertoli cell tumours**

These tumours are well circumscribed, yellow, tan or white in colour, with an average diameter of 3.5 cm [315]. Microscopically, the cells are eosinophilic to pale with vacuolated cytoplasm. The nuclei are regular with grooves and inclusions may be present. The arrangement of the cells is tubular or solid; a cord-like or retiform pattern is possible. The stroma is fine with capillaries, but in some cases a sclerosing aspect predominates. The cells express vimentin, cytokeratins, inhibin (40%) and protein S-100 (30%) [315]. The rate of malignancy ranges between 10% and 22%. Signs of a malignant Sertoli tumour are as follows [317, 318]:

- large size (> 5 cm);
- increased mitotic activity (> 5 per 10 HPF);
- pleomorphic nuclei with nucleoli;
- necrosis;
- vascular invasion.

9.3.2.1 **Classification**

Three subtypes have been described [316]:

- classic Sertoli cell tumour [315];
- large cell calcifying form with characteristic calcifications [319, 320];
- sclerosing form [321, 322].

9.3.3 **Diagnosis**

Patients present either with an enlarged testis or the tumour is found incidentally on US. Most classic Sertoli cell tumours are unilateral and unifocal. Hormonal disorders are infrequent, although gynaecomastia is sometimes seen [315]. The testicular tumour-markers AFP, hCG, LDH and PLAP are always negative. Diagnostic work-up must include tumour markers, hormones (at least testosterone, LH and FSH; if not conclusive, also oestrogen, oestradiol, progesterone and cortisol), US of both testes and CT of chest and

abdomen. Sertoli cell tumours are generally hypoechoic on US, but they can be of variant appearance and thus cannot be safely distinguished from germ-cell tumours [316]. Only the large cell calcifying form has a characteristic image with bright echogenic foci due to calcification [323]. Metastatic disease of 12% in classic Sertoli cell tumour has been reported. In general, affected patients are older, tumours are nearly always palpable, and show more than one sign of malignancy [315].

The large cell calcifying form is diagnosed in younger men and is associated with genetic dysplastic syndromes (Carney's complex [324] and Peutz-Jeghers syndrome [325]) or, in about 40% of cases, endocrine disorders. Forty-four percent of cases are bilateral, either synchronous or metachronous, and 28% show multifocality with good prognosis [320].

Up to 20% of the large cell calcifying forms are malignant. It has been suggested that discrimination between an early and late onset type may define a different risk for metastatic disease (5.5% compared to 23%) [316].

The sclerosing subtype is very rare, unilateral, with a mean age around 40 years and metastases are infrequent [322].

9.4 Treatment of Leydig- and Sertoli cell tumours

Asymptomatic, small volume testicular tumours are often misinterpreted as germ-cell tumours, and inguinal orchidectomy is performed. An organ-sparing procedure in every small US-detected, nonpalpable intraparenchymal lesion is highly recommended in order to obtain a histological diagnosis. The incidence of benign definitive histology is high at approximately 80% [326]. In patients with symptoms of gynaecomastia or hormonal disorders, a non-germ-cell tumour should be considered and immediate orchidectomy avoided. In cases with germ-cell tumour in either frozen section or paraffin histology, orchidectomy is recommended as long as a contralateral normal testicle is present.

When diagnosed and treated early, long-term favourable outcomes are seen at follow-up in Leydig cell tumours, even with its potential metastatic behaviour. In stromal tumours with histological signs of malignancy, especially in older patients, orchidectomy and early retroperitoneal lymphadenectomy may be an option to prevent metastases [113, 327] or to achieve long-term cure in stage IIA cases [328]. Prophylactic RPLND is unjustified for patients with CS I disease without high-risk features [329].

Tumours that have metastasised to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor [113, 327]. No recommendations are available for the treatment of these patients.

9.5 Follow-up of Leydig- and Sertoli cell tumours

Without clinical signs of malignancy, an individualised surveillance strategy after orchidectomy is recommended in patients with one, or more, pathological features of malignancy. Follow-up is recommended in all high-risk patients; every three to six months with physical examination, hormone assays, scrotal and abdominal US, chest radiography, and CT [307].

9.6 Granulosa cell tumour

This is a rare tumour with two variants: juvenile and adult. Less than 100 cases are reported with a predominance of the juvenile type.

- The juvenile type is benign. It is the most frequent congenital testicular tumour and represents about 1-5% of all pre-pubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type [330, 331].
- The average age of the adult type at presentation is 45 years. The typical morphology is a homogeneous, yellow-grey tumour, with elongated cells with grooves in microfollicular and Call-Exner body arrangements [332].

Malignant tumours represent around 20% of cases. Lymphovascular invasion, necrosis, infiltrative borders and size > 4 cm may help in identifying cases with aggressive behaviour. Mitotic counts vary and do not appear to be of prognostic significance [333].

9.7 Thecoma/fibroma group of tumours

These tumours are rare with variable histology such as minimal invasion into surrounding testis, high cellularity, and increased mitotic rate. Their immunoprofile is variable and typically not diagnostic. They seem to be uniformly benign [334].

9.8 Other sex cord/gonadal stromal tumours

Sex cord/gonadal stromal tumours may be incompletely differentiated or in mixed forms. There is limited experience with incompletely differentiated sex cord/gonadal stromal tumours and no reported cases of metastasis [37]. In mixed tumour forms, all the histological components should be reported. However, the clinical behaviour most likely reflects the predominant pattern or the most aggressive component of the tumour [335].

9.9 Tumours containing germ cell and sex cord/gonadal stroma (gonadoblastoma)

Some patients with disorders of sex development (DSDs) have abnormal gonadal development with ambiguous genitalia and an increased risk of germ-cell tumours. If the arrangement of the germ cells is in a nested pattern and the rest of the tumour is composed of sex cord/gonadal stroma, the term gonadoblastoma is used. Bilateral tumours are present in 40% of cases. The prognosis correlates with the invasive growth of the germinal component [336, 337].

In the case of a diffuse arrangement of the different components, there are some doubts about the neoplastic nature of the germinal cells and some authors consider them to be entrapped rather than neoplastic [338].

9.10 Miscellaneous tumours of the testis

9.10.1 Tumours of ovarian epithelial types

These tumours resemble epithelial tumours of the ovary. A cystic appearance with occasional mucinous material can be observed. Microscopically, the aspect is identical to their ovarian counterparts, and their evolution is similar to that of the different epithelial ovarian subtypes. Some Brenner types are malignant [64].

9.10.2 Tumours of the collecting ducts and rete testis

These tumours are very rare. Benign (adenoma) and malignant (adenocarcinoma) variants have been reported, with malignant tumours showing local growth with a mortality rate of 40% within one year [339].

9.10.3 Tumours (benign and malignant) of non-specific stroma

These are very uncommon and have similar criteria, prognosis and treatment to soft tissue sarcomas.

10. REFERENCES

1. Albers, P., *et al.* Guidelines on Testicular Cancer: 2015 Update. *Eur Urol*, 2015. 68: 1054.
<https://www.ncbi.nlm.nih.gov/pubmed/26297604>
2. Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
3. Marconi, L., *et al.* Tumour size and rete testis invasion in the radical orchiectomy specimens of patients with clinical stage I seminoma testis undergoing active surveillance risk factors for developing disease recurrence. PROSPERO International prospective register of systematic reviews, 2017.
https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017056975.
4. La Vecchia, C., *et al.* Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. *Ann Oncol*, 2010. 21: 1323.
<https://www.ncbi.nlm.nih.gov/pubmed/19948741>
5. Rosen, A., *et al.* Global trends in testicular cancer incidence and mortality. *Eur Urol*, 2011. 60: 374.
<https://www.ncbi.nlm.nih.gov/pubmed/21612857>
6. Jemal, A., *et al.* Cancer statistics, 2009. *CA Cancer J Clin*, 2009. 59: 225.
<https://www.ncbi.nlm.nih.gov/pubmed/19474385>
7. Nigam, M., *et al.* Increasing incidence of testicular cancer in the United States and Europe between 1992 and 2009. *World J Urol*, 2014.
<https://www.ncbi.nlm.nih.gov/pubmed/25030752>
8. Ghazarian, A.A., *et al.* Recent trends in the incidence of testicular germ cell tumors in the United States. *Andrology*, 2015. 3: 13.
<https://www.ncbi.nlm.nih.gov/pubmed/25331158>
9. Hoffmann, R., *et al.* Innovations in health care and mortality trends from five cancers in seven European countries between 1970 and 2005. *Int J Public Health*, 2014. 59: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/23989709>

10. Zengerling, F., *et al.* German second-opinion network for testicular cancer: sealing the leaky pipe between evidence and clinical practice. *Oncol Rep*, 2014. 31: 2477.
<https://www.ncbi.nlm.nih.gov/pubmed/24788853>
11. Jones, A., *et al.* Is surveillance for stage 1 germ cell tumours of the testis appropriate outside a specialist centre? *BJU Int*, 1999. 84: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/10444129>
12. Collette, L., *et al.* Impact of the treating institution on survival of patients with "poor-prognosis" metastatic nonseminoma. European Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group and the Medical Research Council Testicular Cancer Working Party. *J Natl Cancer Inst*, 1999. 91: 839.
<https://www.ncbi.nlm.nih.gov/pubmed/10340903>
13. Capitanio, U., *et al.* Population-based study of perioperative mortality after retroperitoneal lymphadenectomy for nonseminomatous testicular germ cell tumors. *Urology*, 2009. 74: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/19501893>
14. Flechon, A., *et al.* Long-term oncological outcome after post-chemotherapy retroperitoneal lymph node dissection in men with metastatic nonseminomatous germ cell tumour. *BJU Int*, 2010. 106: 779.
<https://www.ncbi.nlm.nih.gov/pubmed/20089110>
15. Schrader, M., *et al.* Burden or relief: do second-opinion centers influence the quality of care delivered to patients with testicular germ cell cancer? *Eur Urol*, 2010. 57: 867.
<https://www.ncbi.nlm.nih.gov/pubmed/19931248>
16. Bosl, G.J., *et al.* Testicular germ-cell cancer. *N Engl J Med*, 1997. 337: 242.
<https://www.ncbi.nlm.nih.gov/pubmed/9227931>
17. Kuczyk, M.A., *et al.* Alterations of the p53 tumor suppressor gene in carcinoma in situ of the testis. *Cancer*, 1996. 78: 1958.
<https://www.ncbi.nlm.nih.gov/pubmed/8909317>
18. Andreassen, K.E., *et al.* Genetic variation in AKT1, PTEN and the 8q24 locus, and the risk of testicular germ cell tumor. *Hum Reprod*, 2013. 28: 1995.
<https://www.ncbi.nlm.nih.gov/pubmed/23639623>
19. Chung, C.C., *et al.* Meta-analysis identifies four new loci associated with testicular germ cell tumor. *Nat Genet*, 2013. 45: 680.
<https://www.ncbi.nlm.nih.gov/pubmed/23666239>
20. Looijenga, L.H., *et al.* Relevance of microRNAs in normal and malignant development, including human testicular germ cell tumours. *Int J Androl*, 2007. 30: 304.
<https://www.ncbi.nlm.nih.gov/pubmed/17573854>
21. Reuter, V.E. Origins and molecular biology of testicular germ cell tumors. *Mod Pathol*, 2005. 18 Suppl 2: S51.
<https://www.ncbi.nlm.nih.gov/pubmed/15761466>
22. Jorgensen, N., *et al.* Testicular dysgenesis syndrome comprises some but not all cases of hypospadias and impaired spermatogenesis. *Int J Androl*, 2010. 33: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/20132348>
23. Lip, S.Z., *et al.* A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. *Arch Dis Child*, 2013. 98: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/23193201>
24. Peng, X., *et al.* The association risk of male subfertility and testicular cancer: a systematic review. *PLoS One*, 2009. 4: e5591.
<https://www.ncbi.nlm.nih.gov/pubmed/19440348>
25. Greene, M.H., *et al.* Familial testicular germ cell tumors in adults: 2010 summary of genetic risk factors and clinical phenotype. *Endocr Relat Cancer*, 2010. 17: R109.
<https://www.ncbi.nlm.nih.gov/pubmed/20228134>
26. Lutke Holzik, M.F., *et al.* Genetic predisposition to testicular germ-cell tumours. *Lancet Oncol*, 2004. 5: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/15172357>
27. Kharazmi, E., *et al.* Cancer Risk in Relatives of Testicular Cancer Patients by Histology Type and Age at Diagnosis: A Joint Study from Five Nordic Countries. *Eur Urol*, 2015. 68: 283.
<https://www.ncbi.nlm.nih.gov/pubmed/25913387>
28. Schaapveld, M., *et al.* Risk and prognostic significance of metachronous contralateral testicular germ cell tumours. *Br J Cancer*, 2012. 107: 1637.
<https://www.ncbi.nlm.nih.gov/pubmed/23059747>

29. Lerro, C.C., *et al.* A systematic review and meta-analysis of the relationship between body size and testicular cancer. *Br J Cancer*, 2010. 103: 1467.
<https://www.ncbi.nlm.nih.gov/pubmed/20978513>
30. Brierley, J.E., *et al.*, The TNM Classification of Malignant Tumours 8th edition. 2016.
<http://www.uicc.org/resources/tnm/publications-resources>
31. Peyret, C. Tumeurs du testicule. Synthèse et recommandations en onco-urologie. [Testicular tumours. Summary of onco-urological recommendations] [Article in French]. *Prog Urol* 1993. 2: 60. [No abstract available].
32. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol*, 1997. 15: 594.
<https://www.ncbi.nlm.nih.gov/pubmed/9053482>
33. Motzer, R.J., *et al.* Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol*, 2007. 25: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/17235042>
34. Fizazi, K., *et al.* Early predicted time to normalization of tumor markers predicts outcome in poor-prognosis nonseminomatous germ cell tumors. *J Clin Oncol*, 2004. 22: 3868.
<https://www.ncbi.nlm.nih.gov/pubmed/15302906>
35. Fizazi, K., *et al.* Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. *Lancet Oncol*, 2014. 15: 1442.
<https://www.ncbi.nlm.nih.gov/pubmed/25456363>
36. Leibovitch, L., *et al.* Improved accuracy of computerized tomography based clinical staging in low stage nonseminomatous germ cell cancer using size criteria of retroperitoneal lymph nodes. *J Urol*, 1995. 154: 1759.
<https://www.ncbi.nlm.nih.gov/pubmed/7563341>
37. Jing, B., *et al.* Metastases to retroperitoneal and pelvic lymph nodes: computed tomography and lymphangiography. *Radiol Clin North Am*, 1982. 20: 511.
<https://www.ncbi.nlm.nih.gov/pubmed/7051132>
38. Husband, J.E., *et al.* Evaluation of computed tomography in the management of testicular teratoma. *Br J Urol*, 1981. 53: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/7237052>
39. Swanson, D.A., Role of retroperitoneal lymphadenectomy (RLDN) when patients with nonseminomatous germ cell testicular tumours are at high risk of needing lymph node surgery plus chemotherapy., in *Lymph Node Surgery in Urology*. International Society of Urology Reports. 1996, Isis Medical Media: Oxford, UK.
40. Ellis, J.H., *et al.* Comparison of NMR and CT imaging in the evaluation of metastatic retroperitoneal lymphadenopathy from testicular carcinoma. *J Comput Assist Tomogr*, 1984. 8: 709.
<https://www.ncbi.nlm.nih.gov/pubmed/6539790>
41. Sohaib, S.A., *et al.* Prospective assessment of MRI for imaging retroperitoneal metastases from testicular germ cell tumours. *Clin Radiol*, 2009. 64: 362.
<https://www.ncbi.nlm.nih.gov/pubmed/19264179>
42. See, W.A., *et al.* Chest staging in testis cancer patients: imaging modality selection based upon risk assessment as determined by abdominal computerized tomography scan results. *J Urol*, 1993. 150: 874.
<https://www.ncbi.nlm.nih.gov/pubmed/8345604>
43. de Wit, M., *et al.* [18F]-FDG-PET in clinical stage I/II non-seminomatous germ cell tumours: results of the German multicentre trial. *Ann Oncol*, 2008. 19: 1619.
<https://www.ncbi.nlm.nih.gov/pubmed/18453520>
44. Huddart, R.A., *et al.* 18fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC Trial TE22--the NCRI Testis Tumour Clinical Study Group. *J Clin Oncol*, 2007. 25: 3090.
<https://www.ncbi.nlm.nih.gov/pubmed/17634488>
45. De Santis, M., *et al.* 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. *J Clin Oncol*, 2004. 22: 1034.
<https://www.ncbi.nlm.nih.gov/pubmed/15020605>

46. Bachner, M., *et al.* 2-(1)(8)fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) for postchemotherapy seminoma residual lesions: a retrospective validation of the SEMPET trial. *Ann Oncol*, 2012. 23: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/21460378>
47. Oechsle, K., *et al.* [18F]Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. *J Clin Oncol*, 2008. 26: 5930.
<https://www.ncbi.nlm.nih.gov/pubmed/19018083>
48. Klepp, O., *et al.* Early clinical stages (CS1, CS1Mk+ and CS2A) of non-seminomatous testis cancer. Value of pre- and post-orchietomy serum tumor marker information in prediction of retroperitoneal lymph node metastases. Swedish-Norwegian Testicular Cancer Project (SWENOTECA). *Ann Oncol*, 1990. 1: 281.
<https://www.ncbi.nlm.nih.gov/pubmed/1702312>
49. Heidenreich, A., *et al.* Contralateral testicular biopsy procedure in patients with unilateral testis cancer: is it indicated? *Semin Urol Oncol*, 2002. 20: 234.
<https://www.ncbi.nlm.nih.gov/pubmed/12489055>
50. Mead, G.M., *et al.* The International Germ Cell Consensus Classification: a new prognostic factor-based staging classification for metastatic germ cell tumours. *Clin Oncol (R Coll Radiol)*, 1997. 9: 207.
<https://www.ncbi.nlm.nih.gov/pubmed/9315391>
51. Germa-Lluch, J.R., *et al.* Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: the experience of the Spanish Germ-Cell Cancer Group (GG). *Eur Urol*, 2002. 42: 553.
<https://www.ncbi.nlm.nih.gov/pubmed/12477650>
52. Moul, J. Timely diagnosis of testicular cancer. *Urol Clin North Am*, 2007. 34: 109.
<https://www.ncbi.nlm.nih.gov/pubmed/17484916>
53. Richie, J.P., *et al.* Ultrasonography as a diagnostic adjunct for the evaluation of masses in the scrotum. *Surg Gynecol Obstet*, 1982. 154: 695.
<https://www.ncbi.nlm.nih.gov/pubmed/7071705>
54. Kim, W., *et al.* US MR imaging correlation in pathologic conditions of the scrotum. *Radiographics*, 2007. 27: 1239.
<https://www.ncbi.nlm.nih.gov/pubmed/17848688>
55. Shaw, J. Diagnosis and treatment of testicular cancer. *Am Fam Physician*, 2008. 77: 469.
<https://www.ncbi.nlm.nih.gov/pubmed/18326165>
56. Angulo, J.C., *et al.* Clinicopathological study of regressed testicular tumors (apparent extragonadal germ cell neoplasms). *J Urol*, 2009. 182: 2303.
<https://www.ncbi.nlm.nih.gov/pubmed/19762049>
57. Mancini, M., *et al.* High prevalence of testicular cancer in azoospermic men without spermatogenesis. *Hum Reprod*, 2007. 22: 1042.
<https://www.ncbi.nlm.nih.gov/pubmed/17220165>
58. Cassidy, F.H., *et al.* MR imaging of scrotal tumors and pseudotumors. *Radiographics*, 2010. 30: 665.
<https://www.ncbi.nlm.nih.gov/pubmed/20462987>
59. Gilligan, T.D., *et al.* American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. *J Clin Oncol*, 2010. 28: 3388.
<https://www.ncbi.nlm.nih.gov/pubmed/20530278>
60. Wanderas, E.H., *et al.* Trends in incidence of testicular cancer in Norway 1955-1992. *Eur J Cancer*, 1995. 31a: 2044.
<https://www.ncbi.nlm.nih.gov/pubmed/8562163>
61. Koshida, K., *et al.* Significance of placental alkaline phosphatase (PLAP) in the monitoring of patients with seminoma. *Br J Urol*, 1996. 77: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/8653285>
62. Dieckmann, K.P., *et al.* Serum Levels of MicroRNA miR-371a-3p: A Sensitive and Specific New Biomarker for Germ Cell Tumours. *Eur Urol*, 2017. 71: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/27495845>
63. Robinson, R., *et al.* Is it safe to insert a testicular prosthesis at the time of radical orchidectomy for testis cancer: an audit of 904 men undergoing radical orchidectomy. *BJU Int*, 2016. 117: 249.
<https://www.ncbi.nlm.nih.gov/pubmed/25168859>
64. Eble J.N., *et al.* Pathology and genetics of tumours of the urinary system and male genital organs in International Agency for Research on Cancer (IARC). 2004, IARC Press: Lyon, France.
<http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb7/index.php>

65. Dieckmann, K.P., *et al.* Prevalence of contralateral testicular intraepithelial neoplasia in patients with testicular germ cell neoplasms. *J Clin Oncol*, 1996. 14: 3126.
<https://www.ncbi.nlm.nih.gov/pubmed/8955658>
66. Ruf, C.G., *et al.* Contralateral biopsies in patients with testicular germ cell tumours: patterns of care in Germany and recent data regarding prevalence and treatment of testicular intra-epithelial neoplasia. *Andrology*, 2015. 3: 92.
<https://www.ncbi.nlm.nih.gov/pubmed/25146646>
67. Andreassen, K.E., *et al.* Risk of metachronous contralateral testicular germ cell tumors: a population-based study of 7,102 Norwegian patients (1953-2007). *Int J Cancer*, 2011. 129: 2867.
<https://www.ncbi.nlm.nih.gov/pubmed/21626506>
68. Harland, S.J., *et al.* Intratubular germ cell neoplasia of the contralateral testis in testicular cancer: defining a high risk group. *J Urol*, 1998. 160: 1353.
<https://www.ncbi.nlm.nih.gov/pubmed/9751353>
69. Taberero, J., *et al.* Incidence of contralateral germ cell testicular tumors in South Europe: report of the experience at 2 Spanish university hospitals and review of the literature. *J Urol*, 2004. 171: 164.
<https://www.ncbi.nlm.nih.gov/pubmed/14665868>
70. Albers, P., *et al.* Clinical course and histopathologic risk factor assessment in patients with bilateral testicular germ cell tumors. *Urology*, 1999. 54: 714.
<https://www.ncbi.nlm.nih.gov/pubmed/10510934>
71. Giwercman, A., *et al.* Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. *J Urol*, 1989. 142: 998.
<https://www.ncbi.nlm.nih.gov/pubmed/2571738>
72. Dieckmann, K.P., *et al.* Diagnosis of contralateral testicular intraepithelial neoplasia (TIN) in patients with testicular germ cell cancer: systematic two-site biopsies are more sensitive than a single random biopsy. *Eur Urol*, 2007. 51: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/16814456>
73. Classen, J., *et al.* Radiotherapy with 16 Gy may fail to eradicate testicular intraepithelial neoplasia: preliminary communication of a dose-reduction trial of the German Testicular Cancer Study Group. *Br J Cancer*, 2003. 88: 828.
<https://www.ncbi.nlm.nih.gov/pubmed/12644817>
74. Souchon, R., *et al.* Contralateral testicular cancer in spite of TIN-negative double biopsies and interval cisplatin chemotherapy. *Strahlenther Onkol*, 2006. 182: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/16673063>
75. Petersen, P.M., *et al.* Effect of graded testicular doses of radiotherapy in patients treated for carcinoma-in-situ in the testis. *J Clin Oncol*, 2002. 20: 1537.
<https://www.ncbi.nlm.nih.gov/pubmed/11896102>
76. Heidenreich, A., *et al.* Testis-preserving surgery in bilateral testicular germ cell tumours. *Br J Urol*, 1997. 79: 253.
<https://www.ncbi.nlm.nih.gov/pubmed/9052478>
77. Dieckmann, K.P., *et al.* Treatment of testicular intraepithelial neoplasia (intratubular germ cell neoplasia unspecified) with local radiotherapy or with platinum-based chemotherapy: a survey of the German Testicular Cancer Study Group. *Ann Oncol*, 2013. 24: 1332.
<https://www.ncbi.nlm.nih.gov/pubmed/23293116>
78. Høe-Hansen, C.E., *et al.* Carcinoma in situ testis, the progenitor of testicular germ cell tumours: a clinical review. *Ann Oncol*, 2005. 16: 863.
<https://www.ncbi.nlm.nih.gov/pubmed/15821122>
79. Screening for testicular cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med*, 2011. 154: 483.
<https://www.ncbi.nlm.nih.gov/pubmed/21464350>
80. Thornton, C.P. Best Practice in Teaching Male Adolescents and Young Men to Perform Testicular Self-Examinations: A Review. *J Pediatr Health Care*, 2016. 30: 518.
<https://www.ncbi.nlm.nih.gov/pubmed/26778347>
81. Warde, P., *et al.* Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. *J Clin Oncol*, 2002. 20: 4448.
<https://www.ncbi.nlm.nih.gov/pubmed/12431967>
82. Aparicio, J., *et al.* Risk-adapted management for patients with clinical stage I seminoma: the Second Spanish Germ Cell Cancer Cooperative Group study. *J Clin Oncol*, 2005. 23: 8717.
<https://www.ncbi.nlm.nih.gov/pubmed/16260698>

83. Chung, P., *et al.* Evaluation of a prognostic model for risk of relapse in stage I seminoma surveillance. *Cancer Med*, 2015. 4: 155.
<https://www.ncbi.nlm.nih.gov/pubmed/25236854>
84. Mortensen, M.S., *et al.* A nationwide cohort study of stage I seminoma patients followed on a surveillance program. *Eur Urol*, 2014. 66: 1172.
<https://www.ncbi.nlm.nih.gov/pubmed/25064686>
85. Aparicio, J., *et al.* Prognostic factors for relapse in stage I seminoma: a new nomogram derived from three consecutive, risk-adapted studies from the Spanish Germ Cell Cancer Group (SGCCG). *Ann Oncol*, 2014. 25: 2173.
<https://www.ncbi.nlm.nih.gov/pubmed/25210015>
86. Albers, P., *et al.* Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: results of the German Testicular Cancer Study Group Trial. *J Clin Oncol*, 2003. 21: 1505.
<https://www.ncbi.nlm.nih.gov/pubmed/12697874>
87. Alexandre, J., *et al.* Stage I non-seminomatous germ-cell tumours of the testis: identification of a subgroup of patients with a very low risk of relapse. *Eur J Cancer*, 2001. 37: 576.
<https://www.ncbi.nlm.nih.gov/pubmed/11290432>
88. Brydoy, M., *et al.* Paternity and testicular function among testicular cancer survivors treated with two to four cycles of cisplatin-based chemotherapy. *Eur Urol*, 2010. 58: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/20395037>
89. Brydoy, M., *et al.* Sperm counts and endocrinological markers of spermatogenesis in long-term survivors of testicular cancer. *Br J Cancer*, 2012. 107: 1833.
<https://www.ncbi.nlm.nih.gov/pubmed/23169336>
90. Jacobsen, K.D., *et al.* Gonadal function and fertility in patients with bilateral testicular germ cell malignancy. *Eur Urol*, 2002. 42: 229.
<https://www.ncbi.nlm.nih.gov/pubmed/12234507>
91. Spermon, J.R., *et al.* Fertility in men with testicular germ cell tumors. *Fertil Steril*, 2003. 79 Suppl 3: 1543.
<https://www.ncbi.nlm.nih.gov/pubmed/12801557>
92. Nieschlag E, B.H., Pharmacology and clinical use of testosterone, in *Testosterone-Action, Deficiency, Substitution.*, B.H.M. Nieschlag E., Editor. 1999, Springer Verlag Berlin-Heidelberg-New York.
93. Skoogh, J., *et al.* Feelings of loss and uneasiness or shame after removal of a testicle by orchidectomy: a population-based long-term follow-up of testicular cancer survivors. *Int J Androl*, 2011. 34: 183.
<https://www.ncbi.nlm.nih.gov/pubmed/20550599>
94. Jungwirth A., *et al.* EAU Guidelines on Male Infertility. Edn presented at the 32nd EAU Annual Meeting in London, in *EAU Guidelines*, E.G. Office, Editor. 2017, EAU Guidelines Office Arnhem, The Netherlands.
95. Cohn-Cedermark, G., *et al.* Surveillance vs. adjuvant therapy of clinical stage I testicular tumors - a review and the SWENOTECA experience. *Andrology*, 2015. 3: 102.
<https://www.ncbi.nlm.nih.gov/pubmed/25270123>
96. Tandstad, T., *et al.* Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). *Ann Oncol*, 2016. 27: 1299.
<https://www.ncbi.nlm.nih.gov/pubmed/27052649>
97. Kollmannsberger, C., *et al.* Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. *J Clin Oncol*, 2015. 33: 51.
<https://www.ncbi.nlm.nih.gov/pubmed/25135991>
98. Groll, R.J., *et al.* A comprehensive systematic review of testicular germ cell tumor surveillance. *Crit Rev Oncol Hematol*, 2007. 64: 182.
<https://www.ncbi.nlm.nih.gov/pubmed/17644403>
99. Aparicio, J., *et al.* Multicenter study evaluating a dual policy of postorchidectomy surveillance and selective adjuvant single-agent carboplatin for patients with clinical stage I seminoma. *Ann Oncol*, 2003. 14: 867.
<https://www.ncbi.nlm.nih.gov/pubmed/12796024>
100. Tandstad, T., *et al.* Management of seminomatous testicular cancer: a binational prospective population-based study from the Swedish norwegian testicular cancer study group. *J Clin Oncol*, 2011. 29: 719.
<https://www.ncbi.nlm.nih.gov/pubmed/21205748>

101. Oliver, R.T., *et al.* Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). *J Clin Oncol*, 2011. 29: 957.
<https://www.ncbi.nlm.nih.gov/pubmed/21282539>
102. Oliver, R.T., *et al.* Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *Lancet*, 2005. 366: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/16039331>
103. Mead, G.M., *et al.* Randomized trials in 2466 patients with stage I seminoma: patterns of relapse and follow-up. *J Natl Cancer Inst*, 2011. 103: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/21212385>
104. Schoffski P, *et al.* Health-related quality of life (QoL) in patients with seminoma stage I treated with either adjuvant radiotherapy (RT) or two cycles of carboplatinum chemotherapy (CT): Results of a randomized phase III trial of the German Interdisciplinary Working Party on Testicular Cancer *J Clin Oncol*, 2007. 25.
http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/5050
105. Fischer, S., *et al.* Outcome of Men With Relapse After Adjuvant Carboplatin for Clinical Stage I Seminoma. *J Clin Oncol*, 2017. 35: 194.
<https://www.ncbi.nlm.nih.gov/pubmed/27893332>
106. Fossa, S.D., *et al.* Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. *J Clin Oncol*, 1999. 17: 1146.
<https://www.ncbi.nlm.nih.gov/pubmed/10561173>
107. Jones WG, *et al.* A randomized trial of two radiotherapy schedules in the adjuvant treatment of stage I seminoma (MRC TE 18). *Eur J Cancer* 2001. 37.: abstr 572. [No abstract available].
[http://www.ejcancer.com/article/S0959-8049\(01\)81064-9/abstract](http://www.ejcancer.com/article/S0959-8049(01)81064-9/abstract)
108. Melchior, D., *et al.* Long term results and morbidity of paraaortic compared with paraaortic and iliac adjuvant radiation in clinical stage I seminoma. *Anticancer Res*, 2001. 21: 2989.
<https://www.ncbi.nlm.nih.gov/pubmed/11712799>
109. Bieri, S., *et al.* Seminoma of the testis: is scrotal shielding necessary when radiotherapy is limited to the para-aortic nodes? *Radiother Oncol*, 1999. 50: 349.
<https://www.ncbi.nlm.nih.gov/pubmed/10392822>
110. van den Belt-Dusebout, A.W., *et al.* Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol*, 2007. 25: 4370.
<https://www.ncbi.nlm.nih.gov/pubmed/17906202>
111. Horwich, A., *et al.* Second cancer risk and mortality in men treated with radiotherapy for stage I seminoma. *Br J Cancer*, 2014. 110: 256.
<https://www.ncbi.nlm.nih.gov/pubmed/24263066>
112. Aparicio, J., *et al.* Risk-adapted treatment in clinical stage I testicular seminoma: the third Spanish Germ Cell Cancer Group study. *J Clin Oncol*, 2011. 29: 4677.
<https://www.ncbi.nlm.nih.gov/pubmed/22042940>
113. Banerji, J.S., *et al.* Patterns of Care and Survival Outcomes for Malignant Sex Cord Stromal Testicular Cancer: Results from the National Cancer Data Base. *J Urol*, 2016. 196: 1117.
<https://www.ncbi.nlm.nih.gov/pubmed/27036305>
114. Freedman, L.S., *et al.* Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. *Lancet*, 1987. 2: 294.
<https://www.ncbi.nlm.nih.gov/pubmed/2886764>
115. Read, G., *et al.* Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. *J Clin Oncol*, 1992. 10: 1762.
<https://www.ncbi.nlm.nih.gov/pubmed/1403057>
116. Klepp, O., *et al.* Prognostic factors in clinical stage I nonseminomatous germ cell tumors of the testis: multivariate analysis of a prospective multicenter study. Swedish-Norwegian Testicular Cancer Group. *J Clin Oncol*, 1990. 8: 509.
<https://www.ncbi.nlm.nih.gov/pubmed/1689773>
117. Kollmannsberger, C., *et al.* Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy. *Ann Oncol*, 2010. 21: 1296.
<https://www.ncbi.nlm.nih.gov/pubmed/19875756>
118. Nichols, C.R., *et al.* Active surveillance is the preferred approach to clinical stage I testicular cancer. *J Clin Oncol*, 2013. 31: 3490.
<https://www.ncbi.nlm.nih.gov/pubmed/24002502>

119. Cullen, M.H., *et al.* Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. *J Clin Oncol*, 1996. 14: 1106.
<https://www.ncbi.nlm.nih.gov/pubmed/8648364>
120. Pont, J., *et al.* Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. *J Clin Oncol*, 1996. 14: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/8636755>
121. Chevreau, C., *et al.* Long-term efficacy of two cycles of BEP regimen in high-risk stage I nonseminomatous testicular germ cell tumors with embryonal carcinoma and/or vascular invasion. *Eur Urol*, 2004. 46: 209.
<https://www.ncbi.nlm.nih.gov/pubmed/15245815>
122. Bohlen, D., *et al.* Fertility and sexual function following orchiectomy and 2 cycles of chemotherapy for stage I high risk nonseminomatous germ cell cancer. *J Urol*, 2001. 165: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/11176393>
123. Huddart, R.A., *et al.* Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J Clin Oncol*, 2003. 21: 1513.
<https://www.ncbi.nlm.nih.gov/pubmed/12697875>
124. Albers, P., *et al.* Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I Nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. *J Clin Oncol*, 2008. 26: 2966.
<https://www.ncbi.nlm.nih.gov/pubmed/18458040>
125. Tandstad, T., *et al.* Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. *J Clin Oncol*, 2009. 27: 2122.
<https://www.ncbi.nlm.nih.gov/pubmed/19307506>
126. Tandstad, T., *et al.* One course of adjuvant BEP in clinical stage I nonseminoma mature and expanded results from the SWENOTECA group. *Ann Oncol*, 2014. 25: 2167.
<https://www.ncbi.nlm.nih.gov/pubmed/25114021>
127. Westermann, D.H., *et al.* Long-term followup results of 1 cycle of adjuvant bleomycin, etoposide and cisplatin chemotherapy for high risk clinical stage I nonseminomatous germ cell tumors of the testis. *J Urol*, 2008. 179: 163.
<https://www.ncbi.nlm.nih.gov/pubmed/18001800>
128. Baniel, J., *et al.* Cost- and risk-benefit considerations in the management of clinical stage I nonseminomatous testicular tumors. *Ann Surg Oncol*, 1996. 3: 86.
<https://www.ncbi.nlm.nih.gov/pubmed/8770308>
129. Rustin, G.J., *et al.* Randomized trial of two or five computed tomography scans in the surveillance of patients with stage I nonseminomatous germ cell tumors of the testis: Medical Research Council Trial TE08, ISRCTN56475197--the National Cancer Research Institute Testis Cancer Clinical Studies Group. *J Clin Oncol*, 2007. 25: 1310.
<https://www.ncbi.nlm.nih.gov/pubmed/17416851>
130. Maroto, P., *et al.* Multicentre risk-adapted management for stage I non-seminomatous germ cell tumours. *Ann Oncol*, 2005. 16: 1915.
<https://www.ncbi.nlm.nih.gov/pubmed/16126737>
131. Tandstad, T., *et al.* Long-term follow-up after risk-adapted treatment in clinical stage 1 (CS1) nonseminomatous germ-cell testicular cancer (NSGCT) implementing adjuvant CVB chemotherapy. A SWENOTECA study. *Ann Oncol*, 2010. 21: 1858.
<https://www.ncbi.nlm.nih.gov/pubmed/20142410>
132. Klepp, O., *et al.* Risk-adapted treatment of clinical stage 1 non-seminoma testis cancer. *Eur J Cancer*, 1997. 33: 1038.
<https://www.ncbi.nlm.nih.gov/pubmed/9376184>
133. Heidenreich, A., *et al.* Complications of primary nerve sparing retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: experience of the German Testicular Cancer Study Group. *J Urol*, 2003. 169: 1710.
<https://www.ncbi.nlm.nih.gov/pubmed/12686815>
134. Nicolai, N., *et al.* Retroperitoneal lymph node dissection with no adjuvant chemotherapy in clinical stage I nonseminomatous germ cell tumours: long-term outcome and analysis of risk factors of recurrence. *Eur Urol*, 2010. 58: 912.
<https://www.ncbi.nlm.nih.gov/pubmed/20817343>

135. Al-Ahmadie, H.A., *et al.* Primary retroperitoneal lymph node dissection in low-stage testicular germ cell tumors: a detailed pathologic study with clinical outcome analysis with special emphasis on patients who did not receive adjuvant therapy. *Urology*, 2013. 82: 1341.
<https://www.ncbi.nlm.nih.gov/pubmed/24094656>
136. Foster, R.S., *et al.* Clinical stage I nonseminoma: surgery versus surveillance. *Semin Oncol*, 1998. 25: 145.
<https://www.ncbi.nlm.nih.gov/pubmed/9562447>
137. Neyer, M., *et al.* Long-term results of laparoscopic retroperitoneal lymph-node dissection for clinical stage I nonseminomatous germ-cell testicular cancer. *J Endourol*, 2007. 21: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/17338618>
138. Krege, S., *et al.* European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part I. *Eur Urol*, 2008. 53: 478.
<https://www.ncbi.nlm.nih.gov/pubmed/18191324>
139. Sheinfeld J, *et al.* Management of postchemotherapy residual masses in advanced germ cell tumours. *Urol Clin North Am* 1997; 18. [No abstract available].
140. Pizzocaro G, *et al.* Marker positive clinical stage I non seminomatous germ cell tumours (NSGCT) of the testis: which primary therapy? *J Urol* 1996. 155(Suppl):328A. [No abstract available].
141. Davis, B.E., *et al.* The management of patients with nonseminomatous germ cell tumors of the testis with serologic disease only after orchiectomy. *J Urol*, 1994. 152: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/7515445>
142. Ahmed, K.A., *et al.* Outcomes and treatment patterns as a function of time in stage IS testicular seminoma: a population-based analysis. *Cancer Epidemiol*, 2014. 38: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/24613492>
143. Classen, J., *et al.* Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. *J Clin Oncol*, 2003. 21: 1101.
<https://www.ncbi.nlm.nih.gov/pubmed/12637477>
144. Chung, P.W., *et al.* Stage II testicular seminoma: patterns of recurrence and outcome of treatment. *Eur Urol*, 2004. 45: 754.
<https://www.ncbi.nlm.nih.gov/pubmed/15149748>
145. Hallemeier, C.L., *et al.* Long-term outcomes of radiotherapy for stage II testicular seminoma--the Mayo Clinic experience. *Urol Oncol*, 2013. 31: 1832.
<https://www.ncbi.nlm.nih.gov/pubmed/22537538>
146. Horwich, A., *et al.* Neoadjuvant carboplatin before radiotherapy in stage IIA and IIB seminoma. *Ann Oncol*, 2013. 24: 2104.
<https://www.ncbi.nlm.nih.gov/pubmed/23592702>
147. Giannatempo, P., *et al.* Radiotherapy or chemotherapy for clinical stage IIA and IIB seminoma: a systematic review and meta-analysis of patient outcomes. *Ann Oncol*, 2015. 26: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/25214543>
148. Krege, S., *et al.* Single agent carboplatin for CS IIA/B testicular seminoma. A phase II study of the German Testicular Cancer Study Group (GTCSG). *Ann Oncol*, 2006. 17: 276.
<https://www.ncbi.nlm.nih.gov/pubmed/16254023>
149. Stephenson, A.J., *et al.* Nonrandomized comparison of primary chemotherapy and retroperitoneal lymph node dissection for clinical stage IIA and IIB nonseminomatous germ cell testicular cancer. *J Clin Oncol*, 2007. 25: 5597.
<https://www.ncbi.nlm.nih.gov/pubmed/18065732>
150. Weissbach, L., *et al.* RPLND or primary chemotherapy in clinical stage IIA/B nonseminomatous germ cell tumors? Results of a prospective multicenter trial including quality of life assessment. *Eur Urol*, 2000. 37: 582.
<https://www.ncbi.nlm.nih.gov/pubmed/10765098>
151. Williams, S.D., *et al.* Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. *N Engl J Med*, 1987. 317: 1433.
<https://www.ncbi.nlm.nih.gov/pubmed/2446132>
152. Horwich, A., *et al.* Primary chemotherapy for stage II nonseminomatous germ cell tumors of the testis. *J Urol*, 1994. 151: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/8254836>
153. Donohue, J.P., *et al.* The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University experience (1965 to 1989). *J Urol*, 1995. 153: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/7966799>

154. Bokemeyer, C., *et al.* Metastatic seminoma treated with either single agent carboplatin or cisplatin-based combination chemotherapy: a pooled analysis of two randomised trials. *Br J Cancer*, 2004. 91: 683.
<https://www.ncbi.nlm.nih.gov/pubmed/15266338>
155. Thibault, C., *et al.* Compliance with guidelines and correlation with outcome in patients with advanced germ-cell tumours. *Eur J Cancer*, 2014. 50: 1284.
<https://www.ncbi.nlm.nih.gov/pubmed/24560488>
156. de Wit, R. Refining the optimal chemotherapy regimen in good prognosis germ cell cancer: interpretation of the current body of knowledge. *J Clin Oncol*, 2007. 25: 4346.
<https://www.ncbi.nlm.nih.gov/pubmed/17906198>
157. Beyer, J., *et al.* [Chemotherapy for germ cell cancer]. *Urologe A*, 2004. 43: 1507.
<https://www.ncbi.nlm.nih.gov/pubmed/15592707>
158. de Wit, R., *et al.* Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. *J Clin Oncol*, 1997. 15: 1837.
<https://www.ncbi.nlm.nih.gov/pubmed/9164193>
159. Horwich, A., *et al.* Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol*, 1997. 15: 1844.
<https://www.ncbi.nlm.nih.gov/pubmed/9164194>
160. de Wit, R., *et al.* Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. *J Clin Oncol*, 2001. 19: 1629.
<https://www.ncbi.nlm.nih.gov/pubmed/11250991>
161. Grimison, P.S., *et al.* Comparison of two standard chemotherapy regimens for good-prognosis germ cell tumors: updated analysis of a randomized trial. *J Natl Cancer Inst*, 2010. 102: 1253.
<https://www.ncbi.nlm.nih.gov/pubmed/20631341>
162. Cary, K.C., *et al.* The impact of bleomycin on retroperitoneal histology at post-chemotherapy retroperitoneal lymph node dissection of good risk germ cell tumors. *J Urol*, 2015. 193: 507.
<https://www.ncbi.nlm.nih.gov/pubmed/25254937>
163. Culine, S., *et al.* Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). *Ann Oncol*, 2007. 18: 917.
<https://www.ncbi.nlm.nih.gov/pubmed/17351252>
164. Kier, M.G., *et al.* Prognostic Factors and Treatment Results After Bleomycin, Etoposide, and Cisplatin in Germ Cell Cancer: A Population-based Study. *Eur Urol*, 2017. 71: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/27649970>
165. Fossa, S.D., *et al.* Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. *J Clin Oncol*, 1998. 16: 716.
<https://www.ncbi.nlm.nih.gov/pubmed/9469362>
166. de Wit, R., *et al.* Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer. *Br J Cancer*, 1998. 78: 828.
<https://www.ncbi.nlm.nih.gov/pubmed/9743309>
167. de Wit, R., *et al.* Randomized phase III study comparing paclitaxel-bleomycin, etoposide, and cisplatin (BEP) to standard BEP in intermediate-prognosis germ-cell cancer: intergroup study EORTC 30983. *J Clin Oncol*, 2012. 30: 792.
<https://www.ncbi.nlm.nih.gov/pubmed/22271474>
168. de Wit, R., *et al.* Management of intermediate-prognosis germ-cell cancer: results of a phase I/II study of Taxol-BEP. *Int J Cancer*, 1999. 83: 831.
<https://www.ncbi.nlm.nih.gov/pubmed/10597204>

169. Nichols, C.R., *et al.* Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. *J Clin Oncol*, 1998. 16: 1287.
<https://www.ncbi.nlm.nih.gov/pubmed/9552027>
170. Droz, J.P., *et al.* Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomised trial. *Eur Urol*, 2007. 51: 739.
<https://www.ncbi.nlm.nih.gov/pubmed/17084512>
171. Daugaard, G., *et al.* A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). *Ann Oncol*, 2011. 22: 1054.
<https://www.ncbi.nlm.nih.gov/pubmed/21059637>
172. Dieckmann, K.P., *et al.* Myocardial infarction and other major vascular events during chemotherapy for testicular cancer. *Ann Oncol*, 2010. 21: 1607.
<https://www.ncbi.nlm.nih.gov/pubmed/20067918>
173. Olofsson, S.E., *et al.* Population-based study of treatment guided by tumor marker decline in patients with metastatic nonseminomatous germ cell tumor: a report from the Swedish-Norwegian Testicular Cancer Group. *J Clin Oncol*, 2011. 29: 2032.
<https://www.ncbi.nlm.nih.gov/pubmed/21482994>
174. Oldenburg, J., *et al.* Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2013. 24 Suppl 6: vi125.
<https://www.ncbi.nlm.nih.gov/pubmed/24078656>
175. Bokemeyer, C., *et al.* Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol*, 2002. 20: 1864.
<https://www.ncbi.nlm.nih.gov/pubmed/11919246>
176. Kollmannsberger, C., *et al.* Identification of prognostic subgroups among patients with metastatic 'IGCCCG poor-prognosis' germ-cell cancer: an explorative analysis using cart modeling. *Ann Oncol*, 2000. 11: 1115.
<https://www.ncbi.nlm.nih.gov/pubmed/11061604>
177. Bokemeyer, C., *et al.* First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: A multivariate and matched-pair analysis. *J Clin Oncol*, 1999. 17: 3450.
<https://www.ncbi.nlm.nih.gov/pubmed/10550141>
178. Massard, C., *et al.* Poor prognosis nonseminomatous germ-cell tumours (NSGCTs): should chemotherapy doses be reduced at first cycle to prevent acute respiratory distress syndrome in patients with multiple lung metastases? *Ann Oncol*, 2010. 21: 1585.
<https://www.ncbi.nlm.nih.gov/pubmed/20181575>
179. Gillessen, S., *et al.* Low-dose induction chemotherapy with Baby-BOP in patients with metastatic germ-cell tumours does not compromise outcome: a single-centre experience. *Ann Oncol*, 2010. 21: 1589.
<https://www.ncbi.nlm.nih.gov/pubmed/20164149>
180. Gerl, A., *et al.* Prognostic implications of tumour marker analysis in non-seminomatous germ cell tumours with poor prognosis metastatic disease. *Eur J Cancer*, 1993. 29A: 961.
<https://www.ncbi.nlm.nih.gov/pubmed/7684597>
181. Murphy, B.A., *et al.* Serum tumor marker decline is an early predictor of treatment outcome in germ cell tumor patients treated with cisplatin and ifosfamide salvage chemotherapy. *Cancer*, 1994. 73: 2520.
<https://www.ncbi.nlm.nih.gov/pubmed/7513603>
182. Andre, F., *et al.* The growing teratoma syndrome: results of therapy and long-term follow-up of 33 patients. *Eur J Cancer*, 2000. 36: 1389.
<https://www.ncbi.nlm.nih.gov/pubmed/10899652>
183. de Wit, R., *et al.* Serum alpha-fetoprotein surge after the initiation of chemotherapy for non-seminomatous testicular cancer has an adverse prognostic significance. *Br J Cancer*, 1998. 78: 1350.
<https://www.ncbi.nlm.nih.gov/pubmed/9823978>
184. Zon, R.T., *et al.* Management strategies and outcomes of germ cell tumor patients with very high human chorionic gonadotropin levels. *J Clin Oncol*, 1998. 16: 1294.
<https://www.ncbi.nlm.nih.gov/pubmed/9552028>

185. Fossa, S.D., *et al.* Prognostic factors in patients progressing after cisplatin-based chemotherapy for malignant non-seminomatous germ cell tumours. *Br J Cancer*, 1999. 80: 1392.
<https://www.ncbi.nlm.nih.gov/pubmed/10424741>
186. Hofmockel, G., *et al.* Chemotherapy in advanced seminoma and the role of postcytostatic retroperitoneal lymph node dissection. *Urol Int*, 1996. 57: 38.
<https://www.ncbi.nlm.nih.gov/pubmed/8840489>
187. Kamat, M.R., *et al.* Value of retroperitoneal lymph node dissection in advanced testicular seminoma. *J Surg Oncol*, 1992. 51: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/1381455>
188. Loehrer, P.J., Sr., *et al.* Chemotherapy of metastatic seminoma: the Southeastern Cancer Study Group experience. *J Clin Oncol*, 1987. 5: 1212.
<https://www.ncbi.nlm.nih.gov/pubmed/2442317>
189. Motzer, R., *et al.* Residual mass: an indication for further therapy in patients with advanced seminoma following systemic chemotherapy. *J Clin Oncol*, 1987. 5: 1064.
<https://www.ncbi.nlm.nih.gov/pubmed/3598610>
190. Herr, H.W., *et al.* Surgery for a post-chemotherapy residual mass in seminoma. *J Urol*, 1997. 157: 860.
<https://www.ncbi.nlm.nih.gov/pubmed/9072586>
191. Mosharafa, A.A., *et al.* Is post-chemotherapy resection of seminomatous elements associated with higher acute morbidity? *J Urol*, 2003. 169: 2126.
<https://www.ncbi.nlm.nih.gov/pubmed/12771733>
192. Puc, H.S., *et al.* Management of residual mass in advanced seminoma: results and recommendations from the Memorial Sloan-Kettering Cancer Center. *J Clin Oncol*, 1996. 14: 454.
<https://www.ncbi.nlm.nih.gov/pubmed/8636757>
193. Miki, T., *et al.* Post-chemotherapy nerve-sparing retroperitoneal lymph node dissection for advanced germ cell tumor. *Int J Urol*, 2009. 16: 379.
<https://www.ncbi.nlm.nih.gov/pubmed/19191930>
194. Carver, B.S., *et al.* Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. *J Clin Oncol*, 2007. 25: 5603.
<https://www.ncbi.nlm.nih.gov/pubmed/17998544>
195. Kollmannsberger, C., *et al.* Management of disseminated nonseminomatous germ cell tumors with risk-based chemotherapy followed by response-guided postchemotherapy surgery. *J Clin Oncol*, 2010. 28: 537.
<https://www.ncbi.nlm.nih.gov/pubmed/20026807>
196. Ehrlich, Y., *et al.* Long-term follow-up of Cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? *J Clin Oncol*, 2010. 28: 531.
<https://www.ncbi.nlm.nih.gov/pubmed/20026808>
197. Hartmann, J.T., *et al.* Comparison of histological results from the resection of residual masses at different sites after chemotherapy for metastatic non-seminomatous germ cell tumours. *Eur J Cancer*, 1997. 33: 843.
<https://www.ncbi.nlm.nih.gov/pubmed/9291803>
198. Hendry, W.F., *et al.* Metastatic nonseminomatous germ cell tumors of the testis: results of elective and salvage surgery for patients with residual retroperitoneal masses. *Cancer*, 2002. 94: 1668.
<https://www.ncbi.nlm.nih.gov/pubmed/11920527>
199. Sheinfeld, J. The role of adjunctive postchemotherapy surgery for nonseminomatous germ-cell tumors: current concepts and controversies. *Semin Urol Oncol*, 2002. 20: 262.
<https://www.ncbi.nlm.nih.gov/pubmed/12489059>
200. Steyerberg, E.W., *et al.* Prediction models for the histology of residual masses after chemotherapy for metastatic testicular cancer. ReHiT Study Group. *Int J Cancer*, 1999. 83: 856.
<https://www.ncbi.nlm.nih.gov/pubmed/10597211>
201. Carver, B.S., *et al.* Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. *J Clin Oncol*, 2007. 25: 1033.
<https://www.ncbi.nlm.nih.gov/pubmed/17261854>
202. Oldenburg, J., *et al.* Postchemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. *J Clin Oncol*, 2003. 21: 3310.
<https://www.ncbi.nlm.nih.gov/pubmed/12947067>

203. Rick, O., *et al.* Residual tumor resection after high-dose chemotherapy in patients with relapsed or refractory germ cell cancer. *J Clin Oncol*, 2004. 22: 3713.
<https://www.ncbi.nlm.nih.gov/pubmed/15365067>
204. Baniel, J., *et al.* Late relapse of clinical stage I testicular cancer. *J Urol*, 1995. 154: 1370.
<https://www.ncbi.nlm.nih.gov/pubmed/7658541>
205. Fizazi, K., *et al.* Assessing prognosis and optimizing treatment in patients with postchemotherapy viable nonseminomatous germ-cell tumors (NSGCT): results of the sCR2 international study. *Ann Oncol*, 2008. 19: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/18042838>
206. Heidenreich, A., *et al.* Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. *Eur Urol*, 2009. 55: 217.
<https://www.ncbi.nlm.nih.gov/pubmed/18926622>
207. Beck, S.D., *et al.* Is full bilateral retroperitoneal lymph node dissection always necessary for postchemotherapy residual tumor? *Cancer*, 2007. 110: 1235.
<https://www.ncbi.nlm.nih.gov/pubmed/17665498>
208. Calestroupat, J.P., *et al.* Postchemotherapy laparoscopic retroperitoneal lymph node dissection in nonseminomatous germ-cell tumor. *J Endourol*, 2009. 23: 645.
<https://www.ncbi.nlm.nih.gov/pubmed/19335332>
209. Busch, J., *et al.* Laparoscopic and open postchemotherapy retroperitoneal lymph node dissection in patients with advanced testicular cancer--a single center analysis. *BMC Urol*, 2012. 12: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/22651395>
210. Arai, Y., *et al.* Extraperitoneal laparoscopic retroperitoneal lymph node dissection after chemotherapy for nonseminomatous testicular germ-cell tumor: surgical and oncological outcomes. *Int Urol Nephrol*, 2012. 44: 1389.
<https://www.ncbi.nlm.nih.gov/pubmed/22648291>
211. Steyerberg, E.W., *et al.* Residual masses after chemotherapy for metastatic testicular cancer: the clinical implications of the association between retroperitoneal and pulmonary histology. Re-analysis of Histology in Testicular Cancer (ReHiT) Study Group. *J Urol*, 1997. 158: 474.
<https://www.ncbi.nlm.nih.gov/pubmed/9224327>
212. Besse, B., *et al.* Nonseminomatous germ cell tumors: assessing the need for postchemotherapy contralateral pulmonary resection in patients with ipsilateral complete necrosis. *J Thorac Cardiovasc Surg*, 2009. 137: 448.
<https://www.ncbi.nlm.nih.gov/pubmed/19185168>
213. Schirren, J., *et al.* The role of residual tumor resection in the management of nonseminomatous germ cell cancer of testicular origin. *Thorac Cardiovasc Surg*, 2012. 60: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/22383152>
214. Ehrlich, Y., *et al.* Vena caval reconstruction during postchemotherapy retroperitoneal lymph node dissection for metastatic germ cell tumor. *Urology*, 2009. 73: 442 e17.
<https://www.ncbi.nlm.nih.gov/pubmed/18436290>
215. Beck, S.D., *et al.* Aortic replacement during post-chemotherapy retroperitoneal lymph node dissection. *J Urol*, 2001. 165: 1517.
<https://www.ncbi.nlm.nih.gov/pubmed/11342909>
216. Winter, C., *et al.* Residual tumor size and IGCCCG risk classification predict additional vascular procedures in patients with germ cell tumors and residual tumor resection: a multicenter analysis of the German Testicular Cancer Study Group. *Eur Urol*, 2012. 61: 403.
<https://www.ncbi.nlm.nih.gov/pubmed/22078334>
217. Wells, H., *et al.* Contemporary retroperitoneal lymph node dissection (RPLND) for testis cancer in the UK - a national study. *BJU Int*, 2017. 119: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/27353395>
218. Eggener, S.E., *et al.* Pathologic findings and clinical outcome of patients undergoing retroperitoneal lymph node dissection after multiple chemotherapy regimens for metastatic testicular germ cell tumors. *Cancer*, 2007. 109: 528.
<https://www.ncbi.nlm.nih.gov/pubmed/17177200>
219. Oechsle, K., *et al.* Long-term survival after treatment with gemcitabine and oxaliplatin with and without paclitaxel plus secondary surgery in patients with cisplatin-refractory and/or multiply relapsed germ cell tumors. *Eur Urol*, 2011. 60: 850.
<https://www.ncbi.nlm.nih.gov/pubmed/21704446>
220. Nicolai, N., *et al.* Long-term results of a combination of paclitaxel, cisplatin and gemcitabine for salvage therapy in male germ-cell tumours. *BJU Int*, 2009. 104: 340.
<https://www.ncbi.nlm.nih.gov/pubmed/19239440>

221. Beck, S.D., *et al.* Outcome analysis for patients with elevated serum tumor markers at postchemotherapy retroperitoneal lymph node dissection. *J Clin Oncol*, 2005. 23: 6149.
<https://www.ncbi.nlm.nih.gov/pubmed/16135481>
222. Fizazi, K., *et al.* Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy--results from an international study group. *J Clin Oncol*, 2001. 19: 2647.
<https://www.ncbi.nlm.nih.gov/pubmed/11352956>
223. Stenning, S.P., *et al.* Postchemotherapy residual masses in germ cell tumor patients: content, clinical features, and prognosis. Medical Research Council Testicular Tumour Working Party. *Cancer*, 1998. 83: 1409.
<https://www.ncbi.nlm.nih.gov/pubmed/9762943>
224. Miller, K.D., *et al.* Salvage chemotherapy with vinblastine, ifosfamide, and cisplatin in recurrent seminoma. *J Clin Oncol*, 1997. 15: 1427.
<https://www.ncbi.nlm.nih.gov/pubmed/9193335>
225. Fizazi, K., *et al.* Combining gemcitabine, cisplatin, and ifosfamide (GIP) is active in patients with relapsed metastatic germ-cell tumors (GCT): a prospective multicenter GETUG phase II trial. *Ann Oncol*, 2014. 25: 987.
<https://www.ncbi.nlm.nih.gov/pubmed/24595454>
226. Pico, J.L., *et al.* A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. *Ann Oncol*, 2005. 16: 1152.
<https://www.ncbi.nlm.nih.gov/pubmed/15928070>
227. Lorch, A., *et al.* Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: a prospective randomized multicenter trial of the German Testicular Cancer Study Group. *J Clin Oncol*, 2007. 25: 2778.
<https://www.ncbi.nlm.nih.gov/pubmed/17602082>
228. Oechsle, K., *et al.* Patterns of relapse after chemotherapy in patients with high-risk non-seminomatous germ cell tumor. *Oncology*, 2010. 78: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/20215785>
229. Agarwala, A.K., *et al.* Salvage chemotherapy with high-dose carboplatin and etoposide with peripheral blood stem cell transplant in patients with relapsed pure seminoma. *Am J Clin Oncol*, 2011. 34: 286.
<https://www.ncbi.nlm.nih.gov/pubmed/20523207>
230. Berger, L.A., *et al.* First salvage treatment in patients with advanced germ cell cancer after cisplatin-based chemotherapy: analysis of a registry of the German Testicular Cancer Study Group (GTCSG). *J Cancer Res Clin Oncol*, 2014. 140: 1211.
<https://www.ncbi.nlm.nih.gov/pubmed/24696231>
231. Massard, C., *et al.* Tumor marker kinetics predict outcome in patients with relapsed disseminated non-seminomatous germ-cell tumors. *Ann Oncol*, 2013. 24: 322.
<https://www.ncbi.nlm.nih.gov/pubmed/23104726>
232. Necchi, A., *et al.* Prognostic impact of progression to induction chemotherapy and prior paclitaxel therapy in patients with germ cell tumors receiving salvage high-dose chemotherapy in the last 10 years: a study of the European Society for Blood and Marrow Transplantation Solid Tumors Working Party. *Bone Marrow Transplant*, 2016. 51: 384.
<https://www.ncbi.nlm.nih.gov/pubmed/26642334>
233. Lorch, A., *et al.* Sequential versus single high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: long-term results of a prospective randomized trial. *J Clin Oncol*, 2012. 30: 800.
<https://www.ncbi.nlm.nih.gov/pubmed/22291076>
234. Mead, G.M., *et al.* A phase II trial of TIP (paclitaxel, ifosfamide and cisplatin) given as second-line (post-BEP) salvage chemotherapy for patients with metastatic germ cell cancer: a medical research council trial. *Br J Cancer*, 2005. 93: 178.
<https://www.ncbi.nlm.nih.gov/pubmed/15999102>
235. Segal, R., *et al.* Surveillance programs for early stage non-seminomatous testicular cancer: a practice guideline. *Can J Urol*, 2001. 8: 1184.
<https://www.ncbi.nlm.nih.gov/pubmed/11268306>
236. Jain, A., *et al.* Phase II clinical trial of oxaliplatin and bevacizumab in refractory germ cell tumors. *Am J Clin Oncol*, 2014. 37: 450.
<https://www.ncbi.nlm.nih.gov/pubmed/23388561>

237. Mego, M., *et al.* Phase II study of everolimus in refractory testicular germ cell tumors. *Urol Oncol*, 2016. 34: 122 e17.
<https://www.ncbi.nlm.nih.gov/pubmed/26612480>
238. Oing, C., *et al.* Investigational targeted therapies for the treatment of testicular germ cell tumors. *Expert Opin Investig Drugs*, 2016. 25: 1033.
<https://www.ncbi.nlm.nih.gov/pubmed/27286362>
239. Necchi, A., *et al.* Combination of paclitaxel, cisplatin, and gemcitabine (TPG) for multiple relapses or platinum-resistant germ cell tumors: long-term outcomes. *Clin Genitourin Cancer*, 2014. 12: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/24161525>
240. Mulherin, B.P., *et al.* Long-term survival with paclitaxel and gemcitabine for germ cell tumors after progression following high-dose chemotherapy with tandem transplant. *Am J Clin Oncol*, 2015. 38: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/26214082>
241. Beyer, J., *et al.* Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. *Ann Oncol*, 2013. 24: 878.
<https://www.ncbi.nlm.nih.gov/pubmed/23152360>
242. Oldenburg, J., *et al.* Late relapses of germ cell malignancies: incidence, management, and prognosis. *J Clin Oncol*, 2006. 24: 5503.
<https://www.ncbi.nlm.nih.gov/pubmed/17158535>
243. Baniel, J., *et al.* Late relapse of testicular cancer. *J Clin Oncol*, 1995. 13: 1170.
<https://www.ncbi.nlm.nih.gov/pubmed/7537800>
244. George, D.W., *et al.* Update on late relapse of germ cell tumor: a clinical and molecular analysis. *J Clin Oncol*, 2003. 21: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/12506179>
245. Oldenburg, J., *et al.* Late recurrences of germ cell malignancies: a population-based experience over three decades. *Br J Cancer*, 2006. 94: 820.
<https://www.ncbi.nlm.nih.gov/pubmed/16508636>
246. Lee, A.H., *et al.* The value of central histopathological review of testicular tumours before treatment. *BJU Int*, 1999. 84: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/10444128>
247. Lipphardt, M.E., *et al.* Late relapse of testicular cancer. *World J Urol*, 2004. 22: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/15064970>
248. Fossa, S.D., *et al.* Treatment outcome of patients with brain metastases from malignant germ cell tumors. *Cancer*, 1999. 85: 988.
<https://www.ncbi.nlm.nih.gov/pubmed/10091779>
249. Bokemeyer, C., *et al.* Treatment of brain metastases in patients with testicular cancer. *J Clin Oncol*, 1997. 15: 1449.
<https://www.ncbi.nlm.nih.gov/pubmed/9193339>
250. Feldman, D.R., *et al.* Brain Metastases in Patients With Germ Cell Tumors: Prognostic Factors and Treatment Options--An Analysis From the Global Germ Cell Cancer Group. *J Clin Oncol*, 2016. 34: 345.
<https://www.ncbi.nlm.nih.gov/pubmed/26460295>
251. Hartmann JT, B.M., Albers P, *et al.* Multidisciplinary treatment and prognosis of patients with central nervous metastases (CNS) from testicular germ cell tumour (GCT) origin. *Proc Ann Soc Clin Oncol*, 2003. 22. [No abstract available].
252. Cathomas, R., *et al.* Interdisciplinary evidence-based recommendations for the follow-up of testicular germ cell cancer patients. *Onkologie*, 2011. 34: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/21346388>
253. Daugaard, G., *et al.* Surveillance for stage I nonseminoma testicular cancer: outcomes and long-term follow-up in a population-based cohort. *J Clin Oncol*, 2014. 32: 3817.
<https://www.ncbi.nlm.nih.gov/pubmed/25267754>
254. Chau, C., *et al.* Treatment outcome and patterns of relapse following adjuvant carboplatin for stage I testicular seminomatous germ-cell tumour: results from a 17-year UK experience. *Ann Oncol*, 2015. 26: 1865.
<https://www.ncbi.nlm.nih.gov/pubmed/26037797>
255. Ko, J.J., *et al.* Conditional Survival of Patients With Metastatic Testicular Germ Cell Tumors Treated With First-Line Curative Therapy. *J Clin Oncol*, 2016. 34: 714.
<https://www.ncbi.nlm.nih.gov/pubmed/26786931>
256. ESMO Testicular Cancer Consensus Conference Guidelines 2017. *Ann Oncol*, prior to print, 2017.

257. Brenner, D.J., *et al.* Computed tomography--an increasing source of radiation exposure. *N Engl J Med*, 2007. 357: 2277.
<https://www.ncbi.nlm.nih.gov/pubmed/18046031>
258. Rathmell, A.J., *et al.* Early detection of relapse after treatment for metastatic germ cell tumour of the testis: an exercise in medical audit. *Clin Oncol (R Coll Radiol)*, 1993. 5: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/7678749>
259. Mortensen, M.S., *et al.* Late Relapses in Stage I Testicular Cancer Patients on Surveillance. *Eur Urol*, 2016. 70: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/26996661>
260. Travis, L.B., *et al.* Testicular cancer survivorship: research strategies and recommendations. *J Natl Cancer Inst*, 2010. 102: 1114.
<https://www.ncbi.nlm.nih.gov/pubmed/20585105>
261. Oldenburg, J., *et al.* Personalizing, not patronizing: The case for patient autonomy by unbiased presentation of management options in stage I testicular cancer. *Ann Oncol*, 2015. 26: 833.
<https://www.ncbi.nlm.nih.gov/pubmed/25378299>
262. Vidal A, T.G., *et al.* Long term outcome of patients with clinical stage I high-risk nonseminomatous germ cell tumors 15 years after one adjuvant cycle of Bleomycin, Etoposide and Cisplatin chemotherapy. *Ann Oncol*, 2015. 26: 374.
<https://www.ncbi.nlm.nih.gov/pubmed/25392157>
263. Haugnes, H.S., *et al.* Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. *J Clin Oncol*, 2012. 30: 3752.
<https://www.ncbi.nlm.nih.gov/pubmed/23008318>
264. Fossa, S.D., *et al.* Short- and long-term morbidity after treatment for testicular cancer. *BJU Int*, 2009. 104: 1418.
<https://www.ncbi.nlm.nih.gov/pubmed/19840023>
265. Hemminki, K., *et al.* Second cancers after testicular cancer diagnosed after 1980 in Sweden. *Ann Oncol*, 2010. 21: 1546.
<https://www.ncbi.nlm.nih.gov/pubmed/20019089>
266. Richiardi, L., *et al.* Second malignancies among survivors of germ-cell testicular cancer: a pooled analysis between 13 cancer registries. *Int J Cancer*, 2007. 120: 623.
<https://www.ncbi.nlm.nih.gov/pubmed/17096341>
267. Travis, L.B., *et al.* Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst*, 2005. 97: 1354.
<https://www.ncbi.nlm.nih.gov/pubmed/16174857>
268. Wanderas, E.H., *et al.* Risk of subsequent non-germ cell cancer after treatment of germ cell cancer in 2006 Norwegian male patients. *Eur J Cancer*, 1997. 33: 253.
<https://www.ncbi.nlm.nih.gov/pubmed/9135497>
269. Bokemeyer, C., *et al.* Treatment of testicular cancer and the development of secondary malignancies. *J Clin Oncol*, 1995. 13: 283.
<https://www.ncbi.nlm.nih.gov/pubmed/7799032>
270. Fung, C., *et al.* Solid tumors after chemotherapy or surgery for testicular nonseminoma: a population-based study. *J Clin Oncol*, 2013. 31: 3807.
<https://www.ncbi.nlm.nih.gov/pubmed/24043737>
271. Howard, R., *et al.* Risk of leukemia among survivors of testicular cancer: a population-based study of 42,722 patients. *Ann Epidemiol*, 2008. 18: 416.
<https://www.ncbi.nlm.nih.gov/pubmed/18433667>
272. Kollmannsberger, C., *et al.* Secondary leukemia following high cumulative doses of etoposide in patients treated for advanced germ cell tumors. *J Clin Oncol*, 1998. 16: 3386.
<https://www.ncbi.nlm.nih.gov/pubmed/9779717>
273. Nichols, C.R., *et al.* Secondary leukemia associated with a conventional dose of etoposide: review of serial germ cell tumor protocols. *J Natl Cancer Inst*, 1993. 85: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/7677934>
274. Fossa, S.D., *et al.* Noncancer causes of death in survivors of testicular cancer. *J Natl Cancer Inst*, 2007. 99: 533.
<https://www.ncbi.nlm.nih.gov/pubmed/17405998>
275. O'Sullivan, J.M., *et al.* Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. *Ann Oncol*, 2003. 14: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/12488299>

276. Haugnes, H.S., *et al.* Pulmonary function in long-term survivors of testicular cancer. *J Clin Oncol*, 2009. 27: 2779.
<https://www.ncbi.nlm.nih.gov/pubmed/19414680>
277. Lauritsen, J., *et al.* Pulmonary Function in Patients With Germ Cell Cancer Treated With Bleomycin, Etoposide, and Cisplatin. *J Clin Oncol*, 2016. 34: 1492.
<https://www.ncbi.nlm.nih.gov/pubmed/26903578>
278. Piketty, A.C., *et al.* The risk of thrombo-embolic events is increased in patients with germ-cell tumours and can be predicted by serum lactate dehydrogenase and body surface area. *Br J Cancer*, 2005. 93: 909.
<https://www.ncbi.nlm.nih.gov/pubmed/16205699>
279. Gizzi, M., *et al.* Predicting and preventing thromboembolic events in patients receiving cisplatin-based chemotherapy for germ cell tumours. *Eur J Cancer*, 2016. 69: 151.
<https://www.ncbi.nlm.nih.gov/pubmed/27821318>
280. Fossa, S.D., *et al.* Increased mortality rates in young and middle-aged patients with malignant germ cell tumours. *Br J Cancer*, 2004. 90: 607.
<https://www.ncbi.nlm.nih.gov/pubmed/14760372>
281. van den Belt-Dusebout, A.W., *et al.* Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol*, 2006. 24: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/16421423>
282. Haugnes, H.S., *et al.* Components of the metabolic syndrome in long-term survivors of testicular cancer. *Ann Oncol*, 2007. 18: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/17060482>
283. Alberti, K.G., *et al.* The metabolic syndrome--a new worldwide definition. *Lancet*, 2005. 366: 1059.
<https://www.ncbi.nlm.nih.gov/pubmed/16182882>
284. Sprauten, M., *et al.* Impact of long-term serum platinum concentrations on neuro- and ototoxicity in Cisplatin-treated survivors of testicular cancer. *J Clin Oncol*, 2012. 30: 300.
<https://www.ncbi.nlm.nih.gov/pubmed/22184390>
285. Rove, K.O., *et al.* Pathologic Risk Factors for Metastatic Disease in Postpubertal Patients With Clinical Stage I Testicular Stromal Tumors. *Urology*, 2016. 97: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/27538802>
286. Teutsch, C., *et al.* Raynaud's phenomenon as a side effect of chemotherapy with vinblastine and bleomycin for testicular carcinoma. *Cancer Treat Rep*, 1977. 61: 925.
<https://www.ncbi.nlm.nih.gov/pubmed/70274>
287. Adoue, D., *et al.* Bleomycin and Raynaud's phenomenon. *Ann Intern Med*, 1984. 100: 770.
<https://www.ncbi.nlm.nih.gov/pubmed/6201095>
288. Vogelzang, N.J., *et al.* Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. *Ann Intern Med*, 1981. 95: 288.
<https://www.ncbi.nlm.nih.gov/pubmed/6168223>
289. Brydoy, M., *et al.* Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. *J Natl Cancer Inst*, 2009. 101: 1682.
<https://www.ncbi.nlm.nih.gov/pubmed/19940282>
290. Bauer, C.A., *et al.* Cochlear structure and function after round window application of ototoxins. *Hear Res*, 2005. 201: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/15721567>
291. Bokemeyer, C., *et al.* Analysis of risk factors for cisplatin-induced ototoxicity in patients with testicular cancer. *Br J Cancer*, 1998. 77: 1355.
<https://www.ncbi.nlm.nih.gov/pubmed/9579846>
292. Osanto, S., *et al.* Long-term effects of chemotherapy in patients with testicular cancer. *J Clin Oncol*, 1992. 10: 574.
<https://www.ncbi.nlm.nih.gov/pubmed/1372350>
293. Oldenburg, J., *et al.* Genetic variants associated with cisplatin-induced ototoxicity. *Pharmacogenomics*, 2008. 9: 1521.
<https://www.ncbi.nlm.nih.gov/pubmed/18855538>
294. Oldenburg, J., *et al.* Cisplatin-induced long-term hearing impairment is associated with specific glutathione s-transferase genotypes in testicular cancer survivors. *J Clin Oncol*, 2007. 25: 708.
<https://www.ncbi.nlm.nih.gov/pubmed/17228018>
295. Perry, D.J., *et al.* Enhanced bleomycin toxicity during acute renal failure. *Cancer Treat Rep*, 1982. 66: 592.
<https://www.ncbi.nlm.nih.gov/pubmed/6174233>

296. Bennett, W.M., *et al.* Fatal pulmonary bleomycin toxicity in cisplatin-induced acute renal failure. *Cancer Treat Rep*, 1980. 64: 921.
<https://www.ncbi.nlm.nih.gov/pubmed/6160913>
297. Sprauten, M., *et al.* Longitudinal serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels in a population-based sample of long-term testicular cancer survivors. *J Clin Oncol*, 2014. 32: 571.
<https://www.ncbi.nlm.nih.gov/pubmed/24419125>
298. Orre, I.J., *et al.* Chronic cancer-related fatigue in long-term survivors of testicular cancer. *J Psychosom Res*, 2008. 64: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/18374735>
299. Fossa, S.D., *et al.* Quality of life in good prognosis patients with metastatic germ cell cancer: a prospective study of the European Organization for Research and Treatment of Cancer Genitourinary Group/Medical Research Council Testicular Cancer Study Group (30941/TE20). *J Clin Oncol*, 2003. 21: 1107.
<https://www.ncbi.nlm.nih.gov/pubmed/12637478>
300. Sprauten M, *et al.* Fatigue in relation to treatment and gonadal function in a population-based sample of 796 testicular cancer survivors 12 and 19 years after treatment. *J Clin Oncol*, 2014. 32.
<http://meetinglibrary.asco.org/content/134564-144>
301. Albers P, *et al.* Chemotherapy compared to surgery: Quality-of-life analysis of the German prospective multicenter trial in clinical stage I NSGCT (AUO AH 01/94). *J Clin Oncol*, 2014. 32: (suppl; abstr 4563).
<http://meetinglibrary.asco.org/content/133252-144>
302. Kim, I., *et al.* Leydig cell tumors of the testis. A clinicopathological analysis of 40 cases and review of the literature. *Am J Surg Pathol*, 1985. 9: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/3993830>
303. Ulbright T.M., *et al.* Tumors of the Testis, Adnexa, Spermatic Cord, and Scrotum (Atlas of Tumor Pathology, Third Series, Fascicle 25. 1999. [No abstract available].
304. Cheville, J.C., *et al.* Leydig cell tumor of the testis: a clinicopathologic, DNA content, and MIB-1 comparison of nonmetastasizing and metastasizing tumors. *Am J Surg Pathol*, 1998. 22: 1361.
<https://www.ncbi.nlm.nih.gov/pubmed/9808128>
305. McCluggage, W.G., *et al.* Cellular proliferation and nuclear ploidy assessments augment established prognostic factors in predicting malignancy in testicular Leydig cell tumours. *Histopathology*, 1998. 33: 361.
<https://www.ncbi.nlm.nih.gov/pubmed/9822927>
306. Reznik, Y., *et al.* Luteinizing hormone regulation by sex steroids in men with germinal and Leydig cell tumours. *Clin Endocrinol (Oxf)*, 1993. 38: 487.
<https://www.ncbi.nlm.nih.gov/pubmed/8392454>
307. Suardi, N., *et al.* Leydig cell tumour of the testis: presentation, therapy, long-term follow-up and the role of organ-sparing surgery in a single-institution experience. *BJU Int*, 2009. 103: 197.
<https://www.ncbi.nlm.nih.gov/pubmed/18990169>
308. Bozzini, G., *et al.* Long-term follow-up using testicle-sparing surgery for Leydig cell tumor. *Clin Genitourin Cancer*, 2013. 11: 321.
<https://www.ncbi.nlm.nih.gov/pubmed/23317518>
309. Maizlin, Z.V., *et al.* Leydig cell tumors of the testis: gray scale and color Doppler sonographic appearance. *J Ultrasound Med*, 2004. 23: 959.
<https://www.ncbi.nlm.nih.gov/pubmed/15292565>
310. Isidori, A.M., *et al.* Differential diagnosis of nonpalpable testicular lesions: qualitative and quantitative contrast-enhanced US of benign and malignant testicular tumors. *Radiology*, 2014. 273: 606.
<https://www.ncbi.nlm.nih.gov/pubmed/24968192>
311. Manganaro, L., *et al.* A prospective study on contrast-enhanced magnetic resonance imaging of testicular lesions: distinctive features of Leydig cell tumours. *Eur Radiol*, 2015. 25: 3586.
<https://www.ncbi.nlm.nih.gov/pubmed/25981218>
312. Matveev, B.P., *et al.* [Leydig-cell tumors of the testis]. *Urol Nefrol (Mosk)*, 1997: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/9381620>
313. Di Tonno, F., *et al.* Lessons from 52 patients with leydig cell tumor of the testis: the GUONE (North-Eastern Uro-Oncological Group, Italy) experience. *Urol Int*, 2009. 82: 152.
<https://www.ncbi.nlm.nih.gov/pubmed/19322000>

314. Leonhartsberger, N., *et al.* Increased incidence of Leydig cell tumours of the testis in the era of improved imaging techniques. *BJU Int*, 2011. 108: 1603.
<https://www.ncbi.nlm.nih.gov/pubmed/21631694>
315. Young, R.H., *et al.* Sertoli cell tumors of the testis, not otherwise specified: a clinicopathologic analysis of 60 cases. *Am J Surg Pathol*, 1998. 22: 709.
<https://www.ncbi.nlm.nih.gov/pubmed/9630178>
316. Giglio, M., *et al.* Testicular sertoli cell tumours and relative sub-types. Analysis of clinical and prognostic features. *Urol Int*, 2003. 70: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/12660458>
317. Kratzer, S.S., *et al.* Large cell calcifying Sertoli cell tumor of the testis: contrasting features of six malignant and six benign tumors and a review of the literature. *Am J Surg Pathol*, 1997. 21: 1271.
<https://www.ncbi.nlm.nih.gov/pubmed/9351565>
318. Henley, J.D., *et al.* Malignant Sertoli cell tumors of the testis: a study of 13 examples of a neoplasm frequently misinterpreted as seminoma. *Am J Surg Pathol*, 2002. 26: 541.
<https://www.ncbi.nlm.nih.gov/pubmed/11979085>
319. Proppe, K.H., *et al.* Large-cell calcifying Sertoli cell tumor of the testis. *Am J Clin Pathol*, 1980. 74: 607.
<https://www.ncbi.nlm.nih.gov/pubmed/7446466>
320. Plata, C., *et al.* Large cell calcifying Sertoli cell tumour of the testis. *Histopathology*, 1995. 26: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/7541015>
321. Zukerberg, L.R., *et al.* Sclerosing Sertoli cell tumor of the testis. A report of 10 cases. *Am J Surg Pathol*, 1991. 15: 829.
<https://www.ncbi.nlm.nih.gov/pubmed/1719830>
322. Kao, C.S., *et al.* Sclerosing Sertoli cell tumor of the testis: a clinicopathologic study of 20 cases. *Am J Surg Pathol*, 2014. 38: 510.
<https://www.ncbi.nlm.nih.gov/pubmed/24552667>
323. Gierke, C.L., *et al.* Large-cell calcifying Sertoli cell tumor of the testis: appearance at sonography. *AJR Am J Roentgenol*, 1994. 163: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/8037034>
324. Washecka, R., *et al.* Testicular tumors in Carney's complex. *J Urol*, 2002. 167: 1299.
<https://www.ncbi.nlm.nih.gov/pubmed/11832717>
325. Young, S., *et al.* Feminizing Sertoli cell tumors in boys with Peutz-Jeghers syndrome. *Am J Surg Pathol*, 1995. 19: 50.
<https://www.ncbi.nlm.nih.gov/pubmed/7802138>
326. Giannarini, G., *et al.* Organ-sparing surgery for adult testicular tumours: a systematic review of the literature. *Eur Urol*, 2010. 57: 780.
<https://www.ncbi.nlm.nih.gov/pubmed/20116165>
327. Mosharafa, A.A., *et al.* Does retroperitoneal lymph node dissection have a curative role for patients with sex cord-stromal testicular tumors? *Cancer*, 2003. 98: 753.
<https://www.ncbi.nlm.nih.gov/pubmed/12910519>
328. Silberstein, J.L., *et al.* Clinical outcomes of local and metastatic testicular sex cord-stromal tumors. *J Urol*, 2014. 192: 415.
<https://www.ncbi.nlm.nih.gov/pubmed/24518791>
329. Featherstone, J.M., *et al.* Sex cord stromal testicular tumors: a clinical series--uniformly stage I disease. *J Urol*, 2009. 181: 2090.
<https://www.ncbi.nlm.nih.gov/pubmed/19286222>
330. Shukla, A.R., *et al.* Juvenile granulosa cell tumor of the testis:: contemporary clinical management and pathological diagnosis. *J Urol*, 2004. 171: 1900.
<https://www.ncbi.nlm.nih.gov/pubmed/15076304>
331. Zugor, V., *et al.* Congenital juvenile granulosa cell tumor of the testis in newborns. *Anticancer Res*, 2010. 30: 1731.
<https://www.ncbi.nlm.nih.gov/pubmed/20592370>
332. Cornejo, K.M., *et al.* Adult granulosa cell tumors of the testis: a report of 32 cases. *Am J Surg Pathol*, 2014. 38: 1242.
<https://www.ncbi.nlm.nih.gov/pubmed/24705318>
333. Miliaras, D., *et al.* Adult type granulosa cell tumor: a very rare case of sex-cord tumor of the testis with review of the literature. *Case Rep Pathol*, 2013. 2013: 932086.
<https://www.ncbi.nlm.nih.gov/pubmed/23762714>

334. Zhang, M., *et al.* Testicular fibrothecoma: a morphologic and immunohistochemical study of 16 cases. *Am J Surg Pathol*, 2013. 37: 1208.
<https://www.ncbi.nlm.nih.gov/pubmed/23715159>
335. Perito, P.E., *et al.* Sertoli-Leydig cell testicular tumor: case report and review of sex cord/gonadal stromal tumor histogenesis. *J Urol*, 1992. 148: 883.
<https://www.ncbi.nlm.nih.gov/pubmed/1512847>
336. Pleskacova, J., *et al.* Tumor risk in disorders of sex development. *Sex Dev*, 2010. 4: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/20558977>
337. Ulbright, T.M., *et al.* Gonadoblastoma and selected other aspects of gonadal pathology in young patients with disorders of sex development. *Semin Diagn Pathol*, 2014. 31: 427.
<https://www.ncbi.nlm.nih.gov/pubmed/25129544>
338. Ulbright, T.M., *et al.* Sex cord-stromal tumors of the testis with entrapped germ cells: a lesion mimicking unclassified mixed germ cell sex cord-stromal tumors. *Am J Surg Pathol*, 2000. 24: 535.
<https://www.ncbi.nlm.nih.gov/pubmed/10757400>
339. Klotz, T., *et al.* [Carcinoma of the rete testis with lymphogenous metastasis: multimodal treatment]. *Urologe A*, 2012. 51: 409.
<https://www.ncbi.nlm.nih.gov/pubmed/22282103>

11. CONFLICT OF INTEREST

All members of the Testicular Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>.

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EAU Guidelines on Penile Cancer

O.W. Hakenberg (Chair), E. Compérat, S. Minhas,
A. Necchi, C. Protzel, N. Watkin
Guidelines Associate: R. Robinson

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Guidelines on Penile Cancer provides up-to-date information on the diagnosis and management of penile squamous cell carcinoma (SCC).

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Penile Cancer Guidelines Panel consists of an international multi-disciplinary group of clinicians, including a pathologist and an oncologist. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of having penile cancer. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/penile-cancer/>.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the most recent dating back to 2014 [1], as are a number of translations of all versions of the Penile Cancer Guidelines. All documents are available through the EAU website Uroweb: <http://uroweb.org/guideline/penile-cancer/>.

1.4 Publication history

The EAU Penile Cancer Guidelines were first published in 2000 with the most recent full update undertaken in 2014.

2. METHODS

2.1 Data identification

A systematic literature search on penile cancer was performed between August 2008 and November 2013. All articles relating to penile cancer (n = 1,602) in the relevant literature databases were reviewed and 352 papers were considered suitable for addition to the research base of the Guidelines. Fully revised Guidelines were produced using the updated research base, together with several national and international guidelines on penile cancer (National Comprehensive Cancer Network [2], French Association of Urology [3] and the European Society of Medical Oncology [4]). Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guideline/>. A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

This document was subjected to independent peer review prior to publication in 2014.

2.3 Future goals

The results of an ongoing systematic review will be included in the 2018 update of the Penile Cancer Guidelines. This review is performed using standard Cochrane systematic review methodology: <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>.

Ongoing systematic review:

- What are the risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy for penile cancer? [6]

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Definition of penile cancer

Penile carcinoma is usually a SCC, although there are other types of penile cancer (see Table 3). Penile SCC usually arises from the epithelium of the inner prepuce or the glans. Penile SCC exists in several histological subtypes. Its pathology is similar to SCC of the oropharynx, female genitalia (cervix, vagina and vulva) and anus and shares some of their natural history.

3.2 Epidemiology

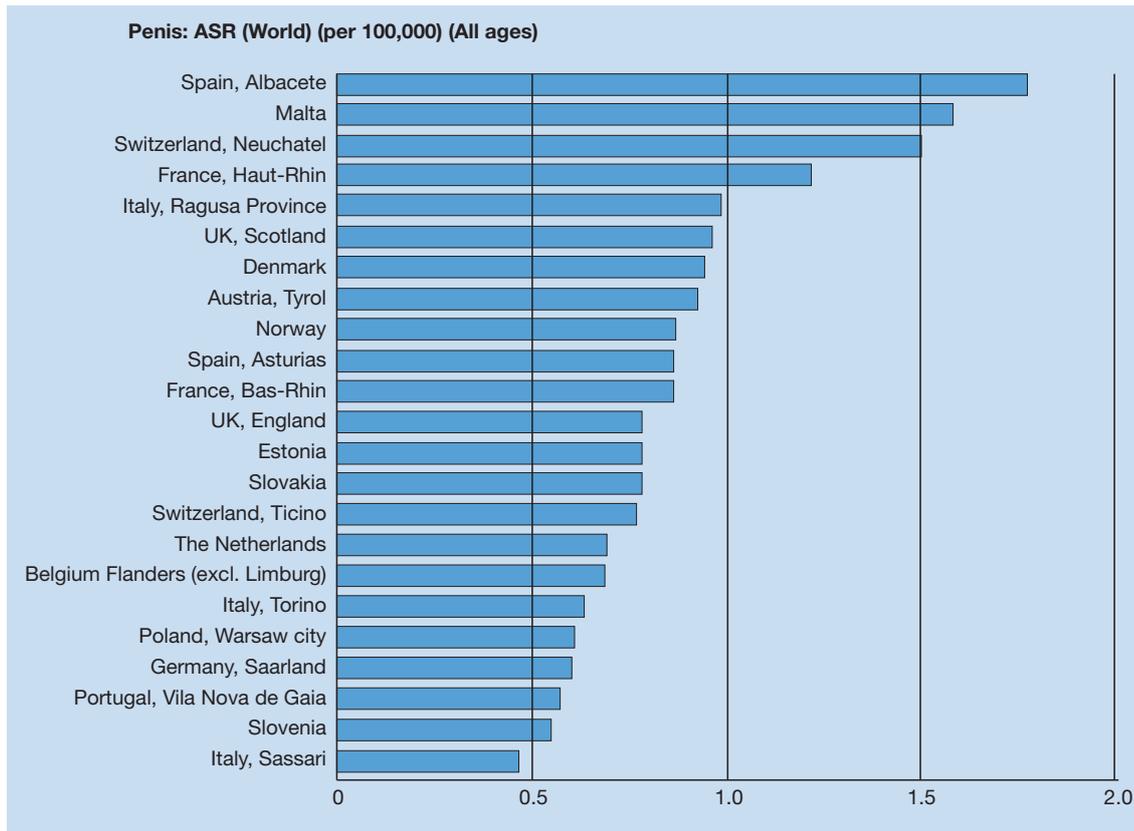
In the Western World, primary penile cancer is uncommon, with an overall incidence of < 1.00/100,000 males in Europe and the USA [7, 8] although there are several geographical areas in Europe with an incidence over 1.00/100,000 (Figure 1) [9]. In North America [7], the incidence of penile cancer is also affected by race and ethnicity, with the incidence highest in white Hispanics (1.01/100,000) compared to Alaskans, Native American Indians (0.77/100,000), African Americans (0.62/100,000) and white non-Hispanics (0.51/100,000), respectively. In contrast, other parts of the world, such as South America, South East Asia and parts of Africa, have a much higher incidence, with penile cancer accounting for 1-2% of malignant diseases in men [9].

Penile cancer is common in regions with a high prevalence of human papilloma virus (HPV), which may account for the variation in incidence, as the worldwide HPV prevalence varies considerably [7]. The annual age-adjusted incidence is 0.7-3.0/100,000 men in India, 8.3/100,000 men in Brazil and even higher in Uganda, where it is the most commonly diagnosed male cancer [9, 10]. The majority of knowledge about penile cancer comes from countries with a high incidence rate.

There is also a less noticeable variation in incidence between European regions (Figure 1). At least one third of cases can be attributed to HPV-related carcinogenesis. There is no data linking penile cancer to human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS).

In the USA, the overall age-adjusted incidence rate decreased from 1973 to 2002 from 0.84/100,000 in 1973-1982 to 0.69/100,000 in 1983-1992, and to 0.58/100,000 in 1993-2002 [7]. In Europe, the overall incidence has been stable from the 1980s until 2013 [8], with an increased incidence reported in Denmark [11] and the UK. A UK longitudinal study confirmed a 21% increase in incidence from 1979-2009 [12].

The incidence of penile cancer increases with age [8]. The peak age is during the sixth decade of life, though the disease does occur in younger men [13].

Figure 1: Annual incidence rate (world standardised) by European region/country*

*Adapted from [9].

3.3 Risk factors and prevention

A review of the published literature from 1966-2000 identified several risk factors for penile cancer [14] (Table 1) (LE: 2a).

Table 1: Recognised aetiological and epidemiological risk factors for penile cancer

Risk factors	Relevance	Ref
Phimosis	Odds ratio 11-16 vs. no phimosis	[15, 16]
Chronic penile inflammation (balanoposthitis related to phimosis) Balinitis xerotica obliterans (lichen sclerosus)	Risk	[17]
Sporalene and ultraviolet A phototherapy for various dermatological conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments	[18]
Smoking	Five-fold increased risk (95% Confidence interval: 2.0-10.1) vs. nonsmokers	[15, 16, 19]
Human papilloma virus infection condylomata acuminata	22.4% in verrucous squamous cell carcinoma 36-66.3% in basaloid-warty	[7, 20]
Rural areas, low socio-economic status, unmarried		[21-24]
Multiple sexual partners, early age of first intercourse	Three to five-fold increased risk of penile cancer	[14, 16, 25]

Human papilloma virus infection (HPV) is an important risk factor; HPV DNA was found in 70-100% of intra-epithelial neoplasia and in 30-40% of invasive penile cancer tissue samples (LE: 2a). It is thought to be a cofactor in the carcinogenesis of some variants of penile SCC [20] through interaction with oncogenes and tumour suppressor genes (P53, Rb genes) [26]. The commonest HPV subtypes in penile cancer are types 16 and 18 [27] and the risk of penile cancer is increased in patients with condyloma acuminata [28] (LE: 2b).

It remains unclear whether HPV-associated penile cancer has a different prognosis to non-HPV-associated penile cancer. A significantly better five-year disease-specific survival (DSS) rate was reported for HPV-positive vs. HPV-negative cases (93% vs. 78%) [29], while others reported no difference in lymph node metastases and ten-year survival rates [30]. There is no direct association between the incidence of penile cancer and cervical cancer. However, both cancers are independently linked with the prevalence of HPV infections [31, 32]. Female sexual partners of patients with penile cancer do not have an increased incidence of cervical cancer.

There is no current recommendation for HPV vaccination in males because of the different HPV-associated risk patterns in penile and cervical cancer. The epidemiological effects of HPV vaccination in girls are also awaited [33, 34].

Phimosis is strongly associated with invasive penile cancer [16, 21, 35, 36], probably due to associated chronic infection since smegma is not a carcinogen [35]. A further risk factor suggested by epidemiological studies is cigarette smoking, 4.5-fold increased risk (95% CI: 2.0-10.1) [36]. The incidence of lichen sclerosus (balanitis xerotica obliterans) in patients with penile cancer is relatively high but is not associated with increased rates of adverse histopathological features, including carcinoma *in situ* (CIS). Other epidemiological risk factors are low levels of socio-economic status and education [21].

Countries and cultures practising routine neonatal circumcision have a lower incidence of penile cancer. Israeli Jews have the lowest incidence at 0.3/100,000/year. Neonatal circumcision removes approximately half the tissue that can develop into penile cancer. A USA study of a 100 matched case-control pairs found that the protective effect of neonatal circumcision against invasive penile cancer (OR 0.41) became much weaker when the comparative analysis was only against men without a history of phimosis (OR 0.79, 95% CI: 0.29-2 [16]). Neonatal circumcision does not reduce the risk of CIS [16].

3.4 Pathology

Squamous cell carcinoma accounts for > 95% of cases of penile malignancies (Tables 2 and 3). It is not known how often SCC is preceded by premalignant lesions (Table 3) [37-40]. Some variants of primary penile cancer have not yet been included in the World Health Organisation (WHO) classification, including pseudohyperplastic carcinoma, carcinoma cuniculatum, pseudoglandular carcinoma, and warty-basaloid carcinoma.

There are many mixed forms of SCC, including the warty-basaloid form (50-60% of mixed penile SCC), usual- verrucous (hybrid), usual-warty, usual-basaloid or usual-papillary and other rarer combinations.

Other penile malignant lesions include melanocytic lesions, mesenchymal tumours, lymphomas and metastases which are unrelated to penile cancer, and rarer. Aggressive penile sarcoma has been reported. Penile metastases from other neoplasias often have a prostatic or colorectal origin.

Table 2: Premalignant penile lesions (precursor lesions)

Lesions sporadically associated with squamous cell carcinoma (SCC) of the penis: <ul style="list-style-type: none"> • Cutaneous horn of the penis • Bowenoid papulosis of the penis • Lichen sclerosus (balanitis xerotica obliterans)
Premalignant lesions (up to one-third transform to invasive SCC): <ul style="list-style-type: none"> • Intra-epithelial neoplasia grade III • Giant condylomata (Buschke-Löwenstein) • Erythroplasia of Queyrat • Bowen's disease • Paget's disease (intra-dermal ADK)

Table 3: Histological subtypes of penile carcinomas, their frequency and outcome

Subtype	Frequency (% of cases)	Prognosis
Common squamous cell carcinoma (SCC)	48-65	Depends on location, stage and grade
Basaloid carcinoma	4-10	Poor prognosis, frequently early inguinal nodal metastasis [41]
Warty carcinoma	7-10	Good prognosis, metastasis rare
Verrucous carcinoma	3-8	Good prognosis, no metastasis
Papillary carcinoma	5-15	Good prognosis, metastasis rare
Sarcomatoid carcinoma	1-3	Very poor prognosis, early vascular metastasis
Mixed carcinoma	9-10	Heterogeneous group
Pseudohyperplastic carcinoma	< 1	Foreskin, related to lichen sclerosus, good prognosis, metastasis not reported
Carcinoma cuniculatum	< 1	Variant of verrucous carcinoma, good prognosis, metastasis not reported
Pseudoglandular carcinoma	< 1	High-grade carcinoma, early metastasis, poor prognosis
Warty-basaloid carcinoma	9-14	Poor prognosis, high metastatic potential [42] (higher than in warty, lower than in basaloid SCC)
Adenosquamous carcinoma	< 1	Central and peri-meatal glans, high-grade carcinoma, high metastatic potential but low mortality
Mucoepidermoid carcinoma	< 1	Highly aggressive, poor prognosis
Clear cell variant of penile carcinoma	1-2	Exceedingly rare, associated with human papilloma virus, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis [43]

3.4.1 **Gross handling of pathology specimens**

Tissue sections must include entire small lesions and at least three to four blocks of larger lesions. Lymph nodes must be included in their entirety to ensure the detection of micrometastases. Surgical margins must also be completely included.

3.4.2 **Pathology report**

The pathology report must include the anatomical site of the primary tumour, the histological type/subtypes, grade, perineural invasion, depth of invasion, vascular invasion (venous/lymphatic), irregular growth and front of invasion, urethral invasion, invasion of corpus spongiosum/cavernosum and surgical margins.

3.4.3 **Grading**

The Tumour, Node, Metastasis (TNM) classification for penile cancer includes tumour grade, due to its prognostic relevance (Table 4). Both Broder's classification and the WHO grading system for grading penile cancer are highly observer dependent and are no longer used [44].

3.4.4 **Pathological prognostic factors**

Carcinomas limited to the foreskin have a better prognosis and lower risk of regional metastasis [45]. Perineural invasion and histological grade are very strong predictors of poor prognosis and cancer-specific mortality [46]. Although tumour grade is a predictor of metastatic spread, it can be difficult to grade heterogeneous tumours. Lymphatic invasion is an independent predictor of metastasis. Venous embolism is often seen in advanced stages.

Types of penile SCC with an excellent prognosis include: verrucous, papillary, warty, pseudohyperplastic and carcinoma cuniculatum. These SCCs are locally destructive, rarely metastasise and have a very low cancer-related mortality.

High-risk SCC variants are the basaloid, sarcomatoid, adenosquamous and poorly differentiated types. They metastasise early and mortality rates are high. The intermediate-risk SCC group comprises the most common SCC, mixed forms and the pleomorphic form of warty carcinomas.

Stage pT3 tumours that invade the distal (glandular) urethra (25% of cases) do not have a worse outcome [47]. However, invasion of the more proximal urethra, also classified as stage pT3, is due to a highly aggressive SCC with a poor prognosis (see Table 3). The inclusion in the one pT2 group of cancers which invade the corpus spongiosum and the corpora cavernosa is confusing clinically as these conditions have very different prognoses. After a mean follow-up of three years, higher rates of local recurrence (35% vs. 17%)

and mortality (30% vs. 21%) were reported in pT2 tumours (n = 72) with tunica or cavernosal involvement vs. glans-only invasion, respectively [48] (LE: 2b). The Panel proposed defining T2a with spongiosum-only invasion and T2b with tunica and/or corpus cavernosum invasion. A similar prognostic difference was observed in a retrospective analysis of 513 patients treated between 1956 and 2006 [49].

Long-term survival is similar in patients with T2 and T3 tumours and in patients with N1 and N2 disease, using the 1987-2002 TNM classification [49] (LE: 2a).

Two nomograms, based only on small numbers, were developed to estimate prognosis in penile cancer. One study suggested that pT1G1 tumours are low-risk tumours, with 0% developing lymph node metastases, in contrast to high-risk pT2/3 G2/3 tumours, with 83% developing lymph node metastases [50]. Remaining tumours were intermediate-risk tumours with 33% developing metastases. Another study reported similar findings and recommended prophylactic lymphadenectomy for high-risk patients [51]. There is also a 'prognostic index', which ranks several pathological parameters (grade, deepest anatomical level, perineural invasion) to predict the likelihood of inguinal lymph node metastases and five-year survival [52]. The lower the score, the higher the probability of 95% survival at five years.

3.4.5 **Penile cancer and HPV**

A high prevalence of HPV infection is found in basaloid (76%), mixed warty-basaloid (82%) and warty penile (39%) SCCs. The commonest HPV-types in penile SCC are HPV 16 (72%), HPV 6 (9%) and HPV 18 (6%). Verrucous and papillary penile SCCs are HPV-negative. Overall, only one-third of penile SCCs show HPV infection, but those that do are usually infected by several HPV strains.

3.4.6 **Molecular biology**

Little is known about the role of chromosomal abnormalities in penile SCC in relation to biological behaviour and patient outcome [25]. Lower DNA copy and alteration numbers are linked to poorer survival. Alterations in the locus 8q24 may play a major role and are implicated in other neoplasms such as prostate cancer [53, 54]. Telomerase activity has been shown in invasive penile carcinoma [55], and some authors have shown that aneuploidy changed according to tumour grade [56].

Epigenetic alterations evaluating the methylation pattern of CpG islands in CDKN2A have been described. CDKN2A encodes for two tumour suppressor proteins (p16INK4A and p14ARF) which control cell growth through Rb and p53 pathways. Poetsch *et al.* showed that 62% of invasive SCC of the penis displayed allelic loss of p16 and 42% displayed promoter hypermethylation. Tumours immunohistochemically negative for p16 showed hypermethylation of and/or loss of heterozygosity (LOH) near the p16INK4A locus. In that study, p16 negativity was linked to lymph node metastasis, in another study to prognosis [57]. Allelic loss of the p53 gene is a frequent event in penile SCC (42%) [58] and p53 expression has been linked to poor prognosis [59]. Another element influencing lymph node metastasis is the metastasis suppressor protein KAI1/CD82; decreased expression of this protein favours lymph node metastasis [60].

3.4.7 **Penile biopsy**

The diagnosis of penile cancer must be confirmed by biopsy. Although penile cancer is usually obvious, very occasionally it may be confused with non-SCC penile carcinoma or inflammatory lesions. Histological confirmation is necessary to guide management when:

- there is doubt about the exact nature of the lesion (e.g. CIS, metastasis or melanoma);
- treatment is planned with topical agents, radiotherapy or laser surgery;
- lymph node treatment is based on pre-operative histological information (risk-adapted strategy).

Biopsy size is important; in biopsies with an average size of 0.1 cm, it is difficult to evaluate the depth of invasion in 91% of biopsies. The grade at biopsy and in the final specimen may differ in up to 30% of cases with failure to detect cancer in 3.5% of cases [37]. Furthermore, vascular and lymphatic tumour emboli were detected in only 9-11% of cases. Although a punch biopsy may be sufficient for superficial lesions, an excisional biopsy is preferred as it should be deep enough to properly assess the degree of invasion and stage.

3.4.8 **Intra-operative frozen sections and surgical margins**

The aim of surgical treatment is complete removal of the penile carcinoma and negative surgical margins. The width of negative surgical margins should follow a risk-adapted strategy based on tumour grade. Negative surgical margins may be confirmed intra-operatively by frozen section [61]. If surgical margins are studied following these criteria (including urethral and periurethral tissue), only 5 mm of tumour-free tissue is sufficient to consider the surgical margins to be negative [62].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 TNM classification

The 2016 UICC TNM classification for penile cancer [63] introduced some changes as compared to prior editions. The T1 category is stratified into two prognostically different risk groups, depending on the presence or absence of lymphovascular invasion, and grading (Table 4). The classification T2 denotes invasion of the corpus spongiosum, while the T3 category is defined as invasion of the corpora cavernosa, recognising the fact that these two invasion patterns differ prognostically [48, 49]. The current pN1 group consists of one or two inguinal lymph node metastases, pN2 is more than two uni- or bilateral metastatic nodes, and pN3 any pelvic nodes, uni- or bilateral as well as any extranodal extension [63].

Retroperitoneal lymph node metastases are extra-regional nodal and therefore distant metastases.

Table 4: 2016 TNM clinical and pathological classification of penile cancer [63]

Clinical classification	
T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
Ta	Non-invasive verrucous carcinoma*
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated (T1G1-2)
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated (T1G3-4)
T2	Tumour invades corpus spongiosum with or without invasion of the urethra
T3	Tumour invades corpus cavernosum with or without invasion of the urethra
T4	Tumour invades other adjacent structures
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph nodes
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy, unilateral or bilateral
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Pathological classification	
The pT categories correspond to the clinical T categories. The pN categories are based upon biopsy or surgical excision	
pN - Regional Lymph Nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in one or two inguinal lymph nodes
pN2	Metastasis in more than two unilateral inguinal nodes or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral extranodal extension of regional lymph node metastasis
pM - Distant Metastasis	
pM0	No distant metastasis
pM1	Distant metastasis
G - Histopathological Grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3-4	Poorly differentiated/undifferentiated

*Verrucous carcinoma not associated with destructive invasion.

5. DIAGNOSTIC EVALUATION AND STAGING

Penile cancer can be cured in over 80% of cases if diagnosed early. Local treatment, although potentially lifesaving, can be mutilating and devastating for the patient's psychological well-being.

5.1 Primary lesion

Penile carcinoma is usually a clinically obvious lesion; however, it may be hidden under a phimosis. Physical examination should include palpation of the penis to assess the extent of local invasion. Ultrasound (US) can give information about infiltration of the corpora [64, 65]. Magnetic resonance imaging (MRI) with an artificially induced erection can help to exclude tumour invasion of the corpora cavernosa if preservation of the penis is planned [66, 67].

5.2 Regional lymph nodes

Careful palpation of both groins for enlarged inguinal lymph nodes must be part of the initial physical examination of patients with penile cancer.

5.2.1 *Non-palpable inguinal nodes*

If there are no palpable lymph nodes, the likelihood of micrometastatic disease is about 25%. Imaging studies are not helpful in staging clinically normal inguinal regions, though imaging may be helpful in obese patients in whom palpation is unreliable or impossible:

- Inguinal US (7.5 MHz) can reveal abnormal nodes with some enlargement. The longitudinal/transverse diameter ratio and absence of the lymph node hilum are findings with relatively high specificity [68].
- Conventional computed tomography (CT) or MRI scans cannot detect micrometastases reliably [69].
- Imaging with ¹⁸F-DG-positron emission tomography (PET)/CT does not detect lymph node metastases < 10 mm [70, 71].

The further diagnostic management of patients with normal inguinal nodes should be guided by pathological risk factors. Lymphovascular invasion, local stage and grade are risk factors for the likelihood of lymphatic metastasis [72, 73]. Existing nomograms are not accurate enough. Invasive lymph node staging is required in patients at intermediate or high risk of lymphatic spread (see Section 6.2).

5.2.2 *Palpable inguinal nodes*

Palpable lymph nodes are highly indicative of lymph node metastases. Physical examination should note the number of palpable nodes on each side and whether these are fixed or mobile. Additional inguinal imaging does not alter management (see Section 6) and is usually not required.

A pelvic CT scan can be used to assess the pelvic lymph nodes. Imaging with ¹⁸F-DG-PET/CT has shown a high sensitivity of 88-100%, with a specificity of 98-100%, for confirming metastatic nodes in patients with palpable inguinal lymph nodes [71, 74].

5.3 Distant metastases

An assessment of distant metastases should be performed in patients with positive inguinal nodes [75-77] (LE: 2b). Computed tomography of the abdomen and pelvis and a chest X-ray are recommended. Thoracic CT is more sensitive than chest X-ray. Positron emission tomography/computed tomography is an option for identifying pelvic nodal and distant metastases in patients with positive inguinal nodes [78]. There is no established tumour marker for penile cancer. The SCC antigen (SCC Ag) is increased in < 25% of penile cancer patients. One study found that SCC Ag did not predict occult metastatic disease, but was an indicator of disease-free survival (DFS) in lymph-node-positive patients [79].

5.4 Summary of evidence and recommendations for the diagnosis and staging of penile cancer

5.4.1 *Summary of evidence for diagnosis*

Examination should include morphology, extent and invasion of penile structures.
Both groins should be examined and the number, laterality and characteristics of nodes recorded.
Computed tomography of chest, abdomen and pelvis is recommended for patients with inguinal lymph node metastasis.
Magnetic resonance imaging (MRI) with artificial erection improves local staging for men being considered for organ preserving surgery.

5.4.2 Recommendations for the diagnosis and staging of penile cancer

Recommendations	GR
Primary tumour	
Perform a physical examination, record morphology, extent and invasion of penile structures.	C
Obtain MRI with artificial erection in cases for which organ-preserving surgery is intended.	
Inguinal lymph nodes	
Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and: <ul style="list-style-type: none"> if nodes are not palpable, offer invasive lymph node staging in high-risk patients; if nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT. 	C
Distant metastases	
In N+ patients, obtain an abdominopelvic CT scan and chest X-ray for systemic staging. Alternatively, stage with a PET/CT scan.	C
In patients with systemic disease or with relevant symptoms, obtain a bone scan.	

6. DISEASE MANAGEMENT

6.1 Treatment of the primary tumour

Treatment of the primary penile cancer lesion aims to remove the tumour completely, while preserving as much of the penis as possible without compromising radicality. Local recurrence has little effect on long-term survival so that organ preservation strategies can be used [80].

The overall quality of the available research evidence is low. There are no randomised controlled trials or observational studies for surgical management of localised penile cancer nor studies comparing surgical and non-surgical modalities.

Penile preservation appears to be superior in functional and cosmetic outcomes. It is the primary treatment method for men with localised penile cancer. However, there are no randomised studies comparing organ-preserving and ablative treatment strategies, only retrospective studies with a LE: 3, or less.

Histological diagnosis with local staging must be obtained in all cases, especially if considering non-surgical treatment modalities. Treatment of the primary tumour and of the regional nodes can be staged. It is mandatory to remove all malignant tissue with negative surgical margins. Patients must be counselled about all relevant treatment modalities.

Local treatment modalities for small and localised penile cancer include excisional surgery, external beam radiotherapy (EBRT), brachytherapy and laser ablation.

6.1.1 Treatment of superficial non-invasive disease (CIS)

For penile CIS, topical chemotherapy with imiquimod or 5-fluorouracil (5-FU) can be an effective first-line treatment. Both agents have relatively low toxicity and adverse events, but efficacy is limited. Complete responses have been reported in up to 57% of CIS cases [81]. Due to the high rate of persistence and/or recurrence, close and long-term surveillance of such patients is required. If topical treatment fails, it should not be repeated.

Laser treatment can be used for CIS. Photodynamic control may be used in conjunction with carbon dioxide (CO₂) laser treatment [82].

Alternatively, total or partial glans resurfacing can be offered as a primary treatment modality for CIS and as a secondary treatment in case of treatment failure with topical chemotherapy or laser therapy. Glans resurfacing is a surgical technique which consists of complete abrasion of the glandular epithelium followed by covering with a split skin graft. With glans resurfacing for presumed non-invasive disease, up to 20% of patients are found to have superficial invasive disease [83].

6.1.2 Treatment of invasive disease confined to the glans (category Ta/T1a)

A penis-preserving strategy is recommended for small and localised invasive lesions (Ta/T1a). It is mandatory to do a biopsy to confirm diagnosis prior to using conservative treatments. All patients must be circumcised before considering conservative non-surgical treatments. For tumours confined to the prepuce, radical circumcision alone may be curative provided that negative surgical margins are confirmed by definitive histology.

For all surgical treatment options, the intra-operative assessment of surgical margins by frozen section is recommended as tumour-positive margins lead to local recurrence [84]. Total removal of the glans (glansectomy) and prepuce has the lowest recurrence rate for the treatment of small penile lesions (2%) [84]. Negative surgical margins are imperative when using penile-conserving treatments and a margin of 5 mm is considered oncologically safe [84, 85].

Treatment choice depends on tumour size, histology, including stage and grade, localisation (especially relative to the meatus) and patient preference as there are no documented differences in long-term local recurrence rates between surgery, laser and radiation therapy.

6.1.3 **Results of different surgical organ-preserving treatments**

There are only retrospective case series for these treatments. The results have been reported heterogeneously; therefore, the database for assessment is of limited quality.

6.1.3.1 *Laser therapy*

Laser ablation is carried out with a neodymium:yttrium-aluminum garnet (Nd:YAG) laser or a CO₂ laser [86-91]. Visualisation may be improved by photodynamic diagnosis.

The results of CO₂ laser treatment have been reported by three studies all from the same institution [86-88]. Laser treatment was given in combination with radiotherapy or chemotherapy to patients with CIS or T1 penile cancers. Follow-up was five years (median) in all three studies. There is some overlap between the cohorts reported, with a total of 195 patients included in these retrospective series.

No cancer-specific deaths were reported. One study reported an estimated cumulative risk of local recurrence at five years of 10% with CIS (n = 106) and 16% with T1 (n = 78) tumours [86]. Taking all three series together, local recurrence ranged from 14% for CIS [88] to 23% for T1 tumours [87]. The reported rate of inguinal nodal recurrence after local CO₂ laser treatment was 0% [88] and 4% [87]. Secondary partial penectomy at ten years was 3% and 10%, depending on the tumour (CIS vs. T1) and whether or not combination treatment had been given [86].

Four studies on the results of Nd:YAG laser treatment [89-92] reported on a total of 150 patients with a follow-up of at least four years. Local recurrence rates at last follow-up ranged across the four studies from 10% [89] to 48% [90]. In one study [91], recurrence-free survival rates were reported as 100%, 95% and 89% at one, two and five years, respectively. Inguinal nodal recurrence was reported in 21% of patients [89]. Cancer-related deaths were reported in 2% [92] and 9% of patients [90], respectively. Three studies from the same institution, probably including overlapping patient cohorts, reported overall survival (OS) rates by censored or uncensored data which ranged from 100% at four years [89] and 95% [91] to 85% [93] at seven years. The rate of secondary partial penectomy after initial Nd:YAG laser treatment was reported as 4% [91] and 45% [90], respectively. Complications, urinary and sexual function outcomes were assessed in only one study with 29 patients [89], none of which reported complications or a change in urinary and sexual function after successful Nd:YAG laser treatment.

Other studies have presented data on a variety of laser treatments with either a CO₂ laser, Nd:YAG laser, a combination of both, or a potassium titanyl phosphate (KTP) laser [94-97], with a mean follow-up of 32-60 months with stages CIS to T3 included. These studies reported on a total of 138 patients.

The cancer-specific survival (CSS) probability at five years was 95% in one study using the Kaplan-Meier method [95]. This was consistent with the finding from another study in which the cancer-specific mortality rate was relatively low at 2% at a mean follow-up of approximately five years [95]. Local recurrence rates were 11% [96], 19% [95] and 26% [97]. In one study recurrence-free survival at five years was estimated to be 88% [95].

6.1.3.2 *Moh's micrographic surgery*

Moh's micrographic surgery is a technique by which histological margins are taken in a geometrical fashion around a cone of excision. This technique has not been widely used. Only two studies reported a total of 66 patients [98, 99]. The original description [98] consisted of 33 consecutive patients treated between 1936 and 1986 and reported on 29 patients with at least five years follow-up. In each study there was one secondary penile amputation and one death from penile cancer. In Moh's series, 79% were cured at five years [98]. In the other series, 68% were recurrence-free after a median of 37 months and 8% had inguinal nodal recurrence and died of the disease [99]. The local recurrence rate was 32% in one series [99].

6.1.3.3 *Glans resurfacing*

Three studies have reported results with glans resurfacing [83, 100, 101] in a total of 71 patients with CIS or T1. The range of the median duration of follow-up in the three studies was 21-30 months. No cancer-specific deaths were reported and the rates of local recurrence were 0% [100] and 6% [101], without reports of nodal recurrence. There were no reported complications.

6.1.3.4 Glansectomy

Results of another relatively new technique, glansectomy, was reported in three studies [84, 102, 103], whilst a fourth study also reported on glans-preserving surgery [103]. A total of 68 patients with a follow-up of 114 months [102] and 63 months [103] were included. One patient (8%) had a local recurrence [102] and six patients (9%) had inguinal nodal metastases. No cancer-specific deaths were reported. Another group reported 87 patients with six local (6.9%), eleven regional (12.6%) and two systemic recurrences (2.3%), during a mean follow-up of 42 months [84].

6.1.3.5 Partial penectomy

Results of partial penectomy were reported in eight rather heterogeneous studies [88, 103-109] with 184 patients, with T1-T3 tumours, and follow-up between 40-194 months. Cancer-specific mortality ranged from 0-27%, with local recurrence rates ranging from 4-50%. The five-year OS rate was reported by three of the studies and ranged from 59-89% [106, 107, 109].

6.1.3.6 Summary of results of surgical techniques

There is insufficient evidence to suggest a difference regarding the outcomes of different penis-sparing strategies, all generally appear to show good oncological outcomes. Although conservative surgery may improve quality of life (QoL), local recurrence is more likely than after radical surgery, e.g. partial penectomy (5-12% vs. 5%). In a large cohort of patients undergoing conservative surgery, isolated local recurrence was 8.9%, with a five-year DSS rate of 91.7%. Tumour grade, stage and lymphovascular invasion appear to be predictors of local recurrence.

6.1.4 Results of radiotherapy for T1 and T2 disease

Radiation treatment of the primary tumour is an alternative organ-preserving approach with good results in selected patients with T1-2 lesions < 4 cm in diameter [110-115] (LE: 2b). External radiotherapy is given with a minimum dose of 60 Gy combined with a brachytherapy boost or brachytherapy on its own [111, 113]. Radiotherapy results are best with penile brachytherapy with local control rates ranging from 70-90% [111, 113]. The American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy reported good tumour control rates, acceptable morbidity and functional organ preservation for penile brachytherapy for T1 and T2 penile cancers [116]. The rates of local recurrence after radiotherapy are higher than after partial penectomy. With local failure after radiotherapy, salvage surgery can achieve local control [117]. Patients with lesions > 4 cm are not candidates for brachytherapy.

Common complications with radiotherapy include urethral stenosis (20-35%), glans necrosis (10-20%) and late fibrosis of the corpora cavernosa [118] (LE: 3). With brachytherapy, meatal stenosis occurs in > 40% of cases.

Table 5: Summary of reported complications and oncological outcomes of local treatments*

Treatment	Complications	Local recurrence	Nodal recurrence	Cancer-specific deaths	References
Neodymium: yttrium-aluminum garnet laser	None reported	10-48%	21%	2-9%	[89-92]
Carbon dioxide laser	Bleeding, meatal stenosis both < 1%	14-23%	2-4%	None reported	[86-88]
Lasers (unspecified)	Bleeding 8%, local infection 2%	11-26%	2%	2-3%	[94-97]
Moh's micrographic surgery	Local infection 3%, meatal stenosis 6%	32%	8%	3-4%	[98, 99]
Glans resurfacing	None reported	4-6%	Not reported	Not reported	[83, 100, 101]
Glansectomy	None reported	8%	9%	None reported	[102, 103]
Partial penectomy	Not reported	4-13%	14-19%	11-27%	[88, 106, 107, 109]
Brachytherapy	Meatal stenosis > 40%	10-30%	Not reported	Not reported	[110, 111, 113]
Radiotherapy	Urethral stenosis 20-35%, glans necrosis 10-20%	Not reported	Not reported	Not reported	[112, 115-118]

*The ranges are the lowest and highest number of occurrences reported in different series.

6.1.5 **Summary of treatment recommendations for non-invasive and localised superficially invasive penile cancer**

6.1.5.1 *Treatment of invasive disease confined to the corpus spongiosum/glans (T2)*

Total glansectomy, with or without resurfacing of the corporeal heads, is recommended [104] (LE: 3). Radiotherapy is an option (see Section 6.1.6). Partial amputation should be considered in patients unfit for reconstructive surgery [117].

6.1.5.2 *Treatment of disease invading the corpora cavernosa and/or urethra (T2/T3)*

Partial amputation with a tumour-free margin and reconstruction is standard [114]. A surgical margin of 5 mm is considered safe [84, 85]. Patients should remain under close follow-up. Radiotherapy is an option.

6.1.5.3 *Treatment of locally advanced disease invading adjacent structures (T3/T4)*

These are relatively rare (Europe 5%, Brazil 13%) [85]. Total penectomy with perineal urethrostomy is standard surgical treatment for T3 tumours [85]. In more advanced disease (T4), neoadjuvant chemotherapy may be advisable, followed by surgery in responders, as in the treatment of patients with fixed enlarged inguinal nodes (see Section 6.2.4). Otherwise, adjuvant chemotherapy or palliative radiotherapy are options (see Sections 6.2.4 and 6.1.6).

6.1.5.4 *Local recurrence after organ-conserving surgery*

A second organ-conserving procedure can be performed if there is no corpus cavernosum invasion [62, 82, 85, 114]. For large or high-stage recurrence, partial or total amputation is required [118]. A total phallic reconstruction may be offered to patients undergoing total/subtotal amputation [119, 120].

6.1.6 **Guidelines for stage-dependent local treatment of penile carcinoma**

Primary tumour	Use organ-preserving treatment whenever possible	LE	GR
Tis	Topical treatment with 5-fluorouracil or imiquimod for superficial lesions with or without photodynamic control.	3	C
	Laser ablation with carbon dioxide (CO ₂) or neodymium:yttrium-aluminium-garnet (Nd:YAG) laser.		
	Glans resurfacing.		
Ta, T1a (G1, G2)	Wide local excision with circumcision, CO ₂ or Nd:YAG laser surgery with circumcision.	3	C
	Laser ablation with CO ₂ or Nd:YAG laser.		
	Glans resurfacing.		
	Glansectomy with reconstructive surgery, with or without skin grafting.		
	Radiotherapy by external beam or as brachytherapy for lesions < 4 cm.		
T1b (G3) and T2 confined to the glans	Wide local excision plus reconstructive surgery, with or without skin grafting.	3	C
	Laser ablation with circumcision.		
	Glansectomy with circumcision and reconstruction.		
	Radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.		
T2 with invasion of the corpora cavernosa	Partial amputation and reconstruction or radiotherapy by external beam or brachytherapy for lesions < 4 cm in diameter.	3	C
T3 with invasion of the urethra	Partial penectomy or total penectomy with perineal urethrostomy.	3	C
T4 with invasion of other adjacent structures	Neoadjuvant chemotherapy followed by surgery in responders. Alternative: palliative external beam radiation.	3	C
Local recurrence after conservative treatment	Salvage surgery with penis-sparing treatment in small recurrences or partial amputation.	3	C
	Large or high-stage recurrence: partial or total amputation.		

6.2 Management of regional lymph nodes

The development of lymphatic metastases in penile cancer follows the route of anatomical drainage. Inguinal and pelvic lymph nodes provide the regional drainage system for the penis, and the superficial and deep inguinal lymph nodes are the first regional nodal group to manifest lymphatic metastatic spread, which can be unilateral or bilateral [80].

All inguinal sentinel nodes appear to be located in the superior and central inguinal zones, with most in the medial superior zone [81]. No lymphatic drainage has been observed from the penis to the two inferior regions of the groin and no direct drainage to the pelvic nodes has been visualised. [82, 83]. These findings confirm earlier studies.

The second regional lymph node groups are the ipsilateral pelvic lymph nodes. Pelvic nodal disease does not seem to occur without ipsilateral inguinal lymph node metastasis and there are no reports of crossover metastatic spread from one inguinal side to the other pelvic side. Further metastatic lymph node spread from the pelvic nodes to para-aortic and para-caval nodes is outside the regional lymph node drainage system of the penis and is classified as systemic metastatic disease.

The management of regional lymph nodes is decisive for long-term patient survival. Cure can be achieved in metastatic disease confined to the regional lymph nodes. Lymphadenectomy is the treatment of choice for inguinal lymph node metastases. Multimodal treatment combining surgery and polychemotherapy is often indicated.

Management of regional lymph nodes is stage-dependent. In clinically node-negative patients (cN0), micrometastatic disease occurs in about 25% of cases and is related to the local tumour stage and grade. In clinically positive lymph nodes (cN1/cN2), metastatic disease is highly likely and no time should be wasted on antibiotic treatment. Enlarged fixed inguinal lymph nodes (cN3) require multimodal treatment by chemotherapy and surgery. Even if present in only one node, capsular penetration and extra-nodal extension in lymph node metastasis carries a high-risk of progression and is classified as pN3, which also requires multimodal treatment.

6.2.1 Management of patients with clinically normal inguinal lymph nodes (cN0)

Risk stratification for the management of patients with clinically normal lymph nodes depends on stage, grade and the presence or absence of lymphovascular invasion in the primary tumour [84]. Tumours with low risk of metastatic disease are those with superficial penile cancer (pTa, pTis) and low grade. pT1 tumours are a heterogeneous risk group: low risk if they are well differentiated (pT1G1) intermediate-risk group (pT1G2) [85] or high risk (pT1G3 and all higher stages).

Early inguinal lymphadenectomy in clinically node-negative patients is far superior for long-term patient survival compared to therapeutic lymphadenectomy when regional nodal recurrence occurs [86, 87]. One prospective study comparing bilateral lymphadenectomy, radiotherapy and surveillance in clinically node-negative patients reported that five-year OS was significantly better with inguinal lymphadenectomy vs. immediate inguinal radiotherapy or that observed with a surveillance strategy (74% vs. 66% and 63%, respectively) [88].

6.2.1.1 Surveillance

The surveillance of regional lymph nodes carries the risk of regional recurrence arising later from existing micrometastatic disease. Patient survival is over 90% with early lymphadenectomy and below 40% with lymphadenectomy for later regional recurrence [89, 90]. This risk must be taken into account when considering surveillance and informing the patient. Surveillance can only be recommended in patients with pTis and pTa penile cancer and with the appropriate caveats in pT1G1 tumours [89-91]. A prerequisite for surveillance is good patient information and compliance.

6.2.1.2 Invasive nodal staging

Staging of the inguinal lymph nodes in cN0 penile cancer requires an invasive procedure since all imaging techniques (US, CT, MRI) are unreliable in excluding small and micrometastatic lymph node involvement. Although CT criteria other than size have been defined for retrospective detection of lymph node metastases, these have not been validated prospectively [92]. Nomograms are unreliable in predicting node involvement [89, 93, 94] (LE: 2b). Fine-needle aspiration cytology does not reliably exclude micrometastatic disease and is not recommended. Instead, pathological risk factors are used to stratify node-negative patients [87, 95] (LE: 2b).

There are two invasive diagnostic procedures, whose efficacy is evidence-based: modified inguinal lymphadenectomy (mILND) and dynamic sentinel-node biopsy (DSNB). Both are standard approaches for invasive diagnosis of inguinal lymph nodes in clinically node-negative patients.

Modified ILND is the standard surgical approach. Both the superficial inguinal lymph nodes from at least the central and both superior Daseler's zones are removed bilaterally [80, 96] (LE: 3), leaving behind the greater saphenous vein.

Dynamic sentinel node biopsy (DSNB) is based on the assumption that primary lymphatic drainage from a penile cancer initially goes to one or only a few inguinal sentinel nodes on each side before further dissemination to more inguinal nodes. Technetium-99m (^{99m}Tc) nanocolloid is injected around the penile cancer site on the day before surgery; patent blue can be injected as well before surgery. A gamma-ray detection probe is used intra-operatively to detect the sentinel node in 97% of cases. The protocol has been standardised for routine use and has a short learning curve [97]. Dynamic sentinel node biopsy has a reported high sensitivity (90-94%) [97, 98] (LE: 2b). In a pooled meta-analysis of eighteen studies, pooled sensitivity was 88%, which improved to 90% with the addition of patent blue [99].

Both methods of invasive regional lymph node staging in cN0 patients may miss micrometastatic disease leading to regional recurrence and greatly reduced long-term survival [86]. The false-negative rate may be as high as 12-15% for DSNB, even in experienced centres [90, 91]. The false-negative rate of mILND is unknown. The patient must be informed of the risk of a false-negative result and the method being used. If lymph node metastasis is found with either method, an ipsilateral radical inguinal lymphadenectomy is indicated.

6.2.2 **Management of patients with palpable inguinal nodes (cN1/cN2)**

With uni- or bilateral palpable inguinal lymph nodes (cN1/cN2), metastatic lymph node disease is very likely and the traditional clinical advice to prescribe antibiotic treatment to exclude lymph node enlargement due to infection is no longer correct. Instead, appropriate oncological diagnosis and treatment should be undertaken without delay before further metastatic spread occurs. In clinically doubtful cases, US-guided fine needle aspiration cytology is an option [121].

With palpably enlarged inguinal lymph nodes, additional staging using imaging is not useful, except in very obese patients. However, CT or MRI can provide information about the pelvic nodal status. ^{18}F -FDG PET/CT can identify additional metastases in lymph-node positive patients [122]. Dynamic sentinel node biopsy is not reliable in patients with palpably enlarged and suspicious inguinal lymph nodes and should not be used [123] (LE: 3).

6.2.2.1 *Radical inguinal lymphadenectomy*

In clinically lymph node positive patients, surgical staging by inguinal lymphadenectomy is indicated. Intra-operative frozen sections may be used to confirm lymph node metastasis, for which an ipsilateral radical inguinal lymphadenectomy is necessary [80, 85].

Radical inguinal lymphadenectomy carries a significant morbidity due to impaired lymph drainage from the legs and often problematic wound healing. Morbidity can be as high as 50% [124] in the presence of significant risk factors such as increased body mass index. However, recent series have reported lower morbidities of about 25% [125, 126] (LE: 2b). Therapeutic radical inguinal lymphadenectomy can be life-saving and should not be underused for fear of associated morbidity [127]. Lymph node density is a prognostic factor [128].

Tissue handling must be meticulous and take into account the absence of smooth muscle in lymphatic vessel walls. Lymphatic vessels therefore cannot be electrocoagulated and must be closed by ligation or possibly liberal use of clips [129, 130]. Post-operative morbidity is reduced by additional measures to improve drainage, such as stockings, bandaging, inguinal pressure dressings or vacuum suction [131] and prophylactic antibiotics. Advanced cases may require reconstructive surgery for primary wound closure.

The most commonly reported complications in recent series were wound infections (1.2-1.4%), skin necrosis (0.6-4.7%), lymphoedema (5-13.9%) and lymphocele formation (2.1-4%) [125, 126].

Laparoscopic and robot-assisted inguinal lymphadenectomy is feasible, but may not provide any advantage [132-135].

6.2.2.2 *Pelvic lymphadenectomy*

Patients with positive pelvic nodes have a worse prognosis compared to patients with only inguinal nodal metastasis (five-year CSS 71.0% vs. 33.2%) [136]. In the same study with 142 node-positive patients, significant risk factors for pelvic nodal metastasis were the number of positive inguinal nodes (cut-off three), the diameter of inguinal metastatic nodes (cut-off 30 mm) and extra-nodal extension. The percentage of pelvic nodal metastases was 0% without any of these risk factors and 57.1% with all three risk factors [136].

If two or more positive lymph nodes, or one node with extracapsular extension (pN3), are found unilaterally, an ipsilateral pelvic lymphadenectomy is indicated. There is no direct lymphatic drainage from penile tumours to the pelvic lymph nodes [137] and lymphadenectomy is therefore not indicated if there is no involvement of inguinal nodes on that side. This recommendation is based on a study in which the rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes and 56% in those with more than three positive inguinal nodes, or if there was extracapsular involvement in at least one inguinal node [85, 138] (LE: 2b).

Pelvic lymphadenectomy may be performed simultaneously or as a secondary procedure following definitive histology. If bilateral pelvic dissection is indicated, it can be performed through a midline suprapubic extraperitoneal incision. It is important to avoid unnecessary delay if these procedures are indicated [139].

6.2.2.3 *Adjuvant treatment*

In patients with pN2/pN3 disease, adjuvant chemotherapy is recommended [140] (see Section 6.3.1). This is because a retrospective study reported long-term DFS of 84% in node-positive patients with adjuvant chemotherapy after radical lymph node surgery vs. 39% in historical controls without chemotherapy after lymphadenectomy [140].

Although adjuvant radiotherapy has been used after inguinal lymphadenectomy, the data are very limited and it is not generally recommended (see Section 6.2.5). There are no data for neoadjuvant inguinal radiotherapy.

6.2.3 **Management of patients with fixed inguinal nodes (cN3)**

Metastatic disease is always present in these cases. Staging by thoracic, abdominal and pelvic CT scan is necessary to assess the presence of further pelvic nodal disease and systemic metastatic disease. In clinically unequivocal cases, histological verification by biopsy is not required. Rare cases with reasonable doubt require an excisional or core needle biopsy.

These patients have a poor prognosis and are unlikely to be cured by surgery alone. Upfront surgery is not generally recommended as it is non-curative and usually destructive. Multimodal treatment with neoadjuvant chemotherapy followed by radical lymphadenectomy in clinically responsive cases is recommended [141-143]. Responders to neoadjuvant chemotherapy with post-chemotherapy surgery have been reported to achieve long-term survival in 37% of cases [141]. There may be individual patients with reasons for upfront surgery followed by adjuvant treatment.

6.2.4 **Management of lymph node recurrence**

Patients with regional recurrence after surveillance should be treated similarly to patients with primary cN1/cN2 disease (see Section 6.2.2). Patients with regional recurrence following negative invasive staging by DSNB or modified inguinal lymphadenectomy already have disordered inguinal lymphatic drainage and are at a high risk of irregular metastatic progression. Patients with inguinal nodal recurrence after therapeutic radical inguinal lymphadenectomy have a five-year CSS rate of 16% [144].

There is no evidence for the best management in such cases. Multimodal treatment with neoadjuvant and/or adjuvant chemotherapy after radical lymph node surgery is advised.

6.2.5 **The role of radiotherapy for the treatment of lymph node disease**

The use of radiotherapy for nodal disease follows tradition and single-institution policies and is not evidence based. Despite the lack of data, radiotherapy is widely used in some European countries to manage regional lymph node metastasis in penile cancer.

It has not been reported that neoadjuvant or adjuvant radiotherapy improves oncological outcome in node-positive penile cancer [145]. One prospective trial found that inguinal node dissection was superior to inguinal radiotherapy [146]. Another study reported poor long-term survival in patients with adjuvant inguinal and pelvic radiotherapy [147]. Adjuvant chemotherapy has been reported to be far superior to adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive patients in one retrospective series [140]. Using the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Program database, treatment results of 2,458 penile cancer patients treated with either surgery alone or surgery plus EBRT showed that the addition of adjuvant radiotherapy 'had neither a harmful nor a beneficial effect on CSS' [148].

Due to the lack of evidence, radiotherapy in the treatment of lymph node disease in penile cancer is not generally recommended. Prophylactic radiotherapy for cN0 disease is not indicated. Adjuvant inguinal radiotherapy may be considered as an option in selected patients with extracapsular nodal extension (cN3) or as a palliative treatment for surgically irresectable disease.

6.2.6 **Guidelines for treatment strategies for nodal metastases**

Regional lymph nodes	Management of regional lymph nodes is fundamental in the treatment of penile cancer	LE	GR
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	2a	B
	> T1G2: invasive lymph node staging by bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy.	2a	B
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.		
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.		
Pelvic lymphadenopathy	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) and if extracapsular nodal metastasis (pN3) is confirmed.	2a	B
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	2b	B
Radiotherapy	Do not use for the treatment of nodal disease in penile cancer.		

6.3 Chemotherapy

6.3.1 **Adjuvant chemotherapy in node-positive patients after radical inguinal lymphadenectomy**

Multimodal treatment can improve patient outcome in many tumour types. Adjuvant chemotherapy after resection of nodal metastases in penile carcinoma has been reported in a few small and heterogeneous series [141, 149-152]. Comparing different small-scale clinical studies is fraught with difficulty.

The value of adjuvant chemotherapy after radical inguinal lymphadenectomy in node-positive penile cancer was demonstrated by an Italian group who reported long-term (DFS) of 84% in 25 consecutive patients treated with twelve adjuvant weekly courses of vincristine, bleomycin, and methotrexate (VBM) during the period 1979-1990 and compared this to a historical control group of 38 consecutive node-positive patients with radical lymphadenectomy (with- or without adjuvant inguinal radiotherapy) who had achieved a DFS rate of only 39% [141].

This group has also published results of a chemotherapy regimen adjuvant to radical lymphadenectomy in stage pN2-3 patients receiving three courses of cisplatin and 5-fluorouracil (5-FU) which they had been using since 1991 with lower toxicity and even better results compared to VBM [151] (LE: 2b). The same group has been using an adjuvant taxane-based regimen since 2004, cisplatin, 5-FU plus paclitaxel or docetaxel (TPF), in nineteen node-positive patients receiving three to four cycles of TPF after resection of pN2-3 disease [152]. Of those patients, 52.6% were disease-free after a median follow up of 42 months and tolerability was good. Results of adjuvant treatment with paclitaxel and cisplatin also improved outcome [153].

The use of adjuvant chemotherapy is recommended, in particular when the administration of the triple combination chemotherapy is feasible, and curative treatment is aimed for (LE: 2b). No data for the adjuvant chemotherapeutic treatment of penile carcinoma in stage pN1 are available. The administration of an adjuvant treatment in pN1 disease is therefore recommended only in clinical trials.

6.3.2 **Neoadjuvant chemotherapy in patients with fixed or relapsed inguinal nodes**

Bulky inguinal lymph node enlargement (cN3) indicates extensive lymphatic metastatic disease. Primary lymph node surgery is not generally recommended (GR: B). Complete surgical resection is unlikely and only a few patients will benefit from surgery alone.

Very limited data is available on neoadjuvant chemotherapy before inguinal lymph node surgery. This approach enables early treatment of likely systemic disease and down-staging of inguinal lymph node disease. Complete surgical treatment is possible with a good clinical response.

Results were modest in retrospective studies of five to twenty patients treated with bleomycin-vincristinemethotrexate (BVM) and bleomycin-methotrexate-cisplatin (BMP) treatments [142, 143, 154] and in the confirmatory BMP trial of the Southwest Oncology Group [155]. However, treatment-related toxicity was unacceptable due to bleomycin-related mortality.

Cisplatin/5-FU (PF) chemotherapy achieved a response rate of 25-50% with more acceptable tolerability [156, 157]. Over a period of 30 years, five different neoadjuvant chemotherapy regimens were used in twenty patients [80], with long-term survival in 37% of chemotherapy responders who underwent surgery. In the European Organisation for Research and Treatment of Cancer study 30992, 26 patients with locally advanced or metastatic disease received irinotecan and cisplatin chemotherapy. Although the study did not meet its primary endpoint (response rate), there were three cases of pathologically complete remissions (pCR) [158].

A phase II trial evaluated treatment with four cycles of neoadjuvant paclitaxel, cisplatin, and ifosfamide (TIP). An objective response was reported in fifteen out of 30 patients, including three pCRs, which was a marginally significant predictor of survival. The estimated median time to progression (TTP) was 8.1 months and the median OS rate was 17.1 months [159] (LE: 2a).

Similarities between penile SCC and head and neck SCC led to the evaluation in penile cancer of chemotherapy regimens with an efficacy in head and neck SCC, including taxanes. The combination of cisplatin and 5-FU plus a taxane has been used in a neoadjuvant and adjuvant setting [152]. An overall objective response rate of 44% was reported in 28 patients treated neoadjuvantly, including 14% pCR (LE: 2b).

Similarly, a Cancer Research UK phase II trial with TPF (using only docetaxel) reported an objective response of 38.5% in 29 locally advanced or metastatic patients, although the study did not meet its primary endpoint. However, there was significant toxicity [160] (LE: 2a).

Overall, these results support the use of neoadjuvant chemotherapy in patients with fixed, unresectable nodal disease, particularly with a triple combination, including cisplatin and a taxane, whenever feasible (LE: 2a).

There are hardly any data concerning radiochemotherapy with lymph-node surgery in penile cancer. Radiochemotherapy should only be offered in clinical trials [161].

6.3.3 **Palliative chemotherapy in advanced and relapsed disease**

A recent retrospective study of individual patient data of 140 men with advanced penile SCC reported that visceral metastases and an ECOG-performance status greater than one were independent prognostic factors, and that cisplatin-based regimens had better outcomes than non-cisplatin-based regimens after adjusting for prognostic factors [162] (LE: 3).

In clinical practice, however, first-line chemotherapy regimens are variable. Before taxanes were introduced, the data were limited by small numbers, patient heterogeneity and its retrospective nature (except for the EORTC trial [158]). Initial response rates ranged from 25% to 100%, with very few sustained responses and very few long-term survivors. The introduction of taxanes into penile cancer chemotherapy has enhanced the activity and efficacy of the regimens used [80, 142, 143, 153-160, 163].

There are virtually no data on second-line chemotherapy in penile cancer. One report using second-line paclitaxel monotherapy reported an initial response rate under 30%. Therefore, this may be a reasonable option; however, no patients survived [164] (LE: 2a; GR: B). Anecdotally, a benefit has been observed by combining cisplatin with gemcitabine [165] (LE: 4).

6.3.4 **Intra-arterial chemotherapy**

Intra-arterial chemotherapy has been trialled in locally advanced cases, especially cisplatin and gemcitabine in small case series [166-169]. Apart from a limited clinical response, outcome was not significantly improved.

6.3.5 **Targeted therapy**

Targeted drugs have been used as second-line treatment and they could be considered as single-agent treatment in refractory cases. Anti-epidermal growth factor receptor (EGFR) targeted monotherapy has been trialled as EGFR is expressed in penile SCC [166, 167] and the assumed similarities with head and neck SCC [166, 167]. There have been other studies, particularly with the anti-EGFR monoclonal antibodies, panitumumab and cetuximab. Some activity of tyrosine kinase inhibitors has been reported as well [169]. Further clinical studies are needed (LE: 4).

6.3.6 **Guidelines for chemotherapy in penile cancer patients**

Recommendations	LE	GR
Treat patients with pN2-3 tumours with adjuvant chemotherapy (three-four cycles of cisplatin, 5-fluorouracil, paclitaxel or docetaxel).	2b	C
Treat patients with non-resectable or recurrent lymph node metastases with neoadjuvant chemotherapy (4 cycles of a cisplatin and taxane-based regimen) followed by radical surgery.	2a	B
Treat patients with systemic disease and a limited metastatic load with chemotherapy.	3	C

7. FOLLOW-UP

7.1 Rationale for follow-up

The early detection of recurrence during follow-up increases the likelihood of curative treatment. Local recurrence does not significantly reduce long-term survival if successfully treated. In contrast, disease that has spread to the inguinal lymph nodes greatly reduces the rate of long-term DSS. Follow-up is also important in the detection and management of treatment-related complications.

Local or regional nodal recurrences usually occur within two years of primary treatment [80]. After five years, all recurrences were either local recurrences or new primary lesions [80]. These results support an intensive follow-up regimen during the first two years, with a less intensive follow up after this for a total of at least five years. Follow up after five years may be omitted in motivated patients reliably able to continue to carry out regular self-examination [80].

7.1.1 *When and how to follow-up*

In patients with negative inguinal nodes after local treatment, follow-up should include physical examination of the penis and the groins for local and/or regional recurrence. Additional imaging has no proven benefit.

Follow up also depends on the primary treatment modality. Histology from the glans should be obtained to confirm disease-free status following laser ablation or topical chemotherapy.

After potentially curative treatment for inguinal nodal metastases, CT or MRI imaging for the detection of systemic disease should be performed at three-monthly intervals for the first two years, so patients can benefit from adjuvant chemotherapy.

Although rarely, late local recurrences may still occur, with life-threatening metastases becoming very unusual after five years. This means regular follow up can be stopped after five years, provided the patient understands the need to report any local changes immediately [170]. In patients unlikely to self-examine, long-term follow up may be necessary.

7.1.2 *Recurrence of the primary tumour*

Local recurrence is more likely with all types of local organ-preserving treatment, i.e. after local excision, laser treatment, brachytherapy and associated therapies. However, it is very unlikely to increase the risk of dying from the disease in contrast to regional recurrence [80, 171]. Local recurrence occurred during the first two years in up to 27% of patients treated with penis-preserving modalities [172]. After partial penectomy, the risk of local recurrence is about 4-5% [80, 171, 172].

Local recurrence is easily detected by physical examination by the patient himself or his physician. Patient education is an essential part of follow-up and the patient should be urged to visit a specialist if any changes are seen.

7.1.3 *Regional recurrence*

Most regional recurrences occur during the first two years after diagnosis and treatment, irrespective of whether a surveillance strategy has been used or a sentinel-node based management or modified inguinal lymphadenectomy.

Although very unlikely, regional recurrence can occur unexpectedly after two years. It is therefore wise to continue close follow up in these patients, for whom self-examination is very important [173]. The highest rate of regional recurrence (9%) occurs in patients managed using a surveillance strategy, while the lowest is in patients who have undergone invasive nodal staging by modified inguinal lymphadenectomy or DSNB and whose lymph nodes were negative (2.3%).

The use of US and fine needle aspiration cytology (FNAC) in suspicious cases has improved the early detection rate of regional recurrence [68, 173, 174]. There are no data to support the routine use of CT or MRI for the follow-up of regional nodes.

Patients who have had surgical treatment for lymph node metastases without adjuvant treatment have an increased risk of regional recurrence of 19% [80]. Regional recurrence requires timely treatment by radical inguinal lymphadenectomy and adjuvant therapy (see Section 6).

7.1.4 Guidelines for follow-up in penile cancer

	Interval of follow-up		Examinations and investigations	Minimum duration of follow-up	GR
	Years one to two	Years three to five			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	Three months	Six months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for carcinoma <i>in situ</i> .	Five years	C
Amputation	Three months	One year	Regular physician or self-examination.	Five years	C
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	Three months	Six months	Regular physician or self-examination.	Five years	C
pN0 at initial treatment	Three months	One year	Regular physician or self-examination. Ultrasound with fine-needle aspiration biopsy optional.	Five years	C
pN+ at initial treatment	Three months	Six months	Regular physician or self-examination. Ultrasound with fine-needle aspiration cytology optional, computed tomography / magnetic resonance imaging optional.	Five years	C

7.2 Quality of life

7.2.1 Consequences after penile cancer treatment

In patients with long-term survival after penile cancer treatment, sexual dysfunction, voiding problems and cosmetic penile appearance may adversely affect the patient's QoL [175]. There is very little data on sexual function and QoL after treatment for penile cancer.

7.2.2 Sexual activity and quality of life after laser treatment

A retrospective interview-based Swedish study after laser treatment for penile CIS [94] in 58 out of 67 surviving patients with a mean age of 63 years, of whom 46 participated, reported a marked decrease in some sexual practices, such as manual stimulation, caressing and fellatio, but a general satisfaction rate with life overall including their sex lives, similar to that of the general Swedish population.

A large study on CO₂ laser treatment of penile cancer in 224 patients reported no problems with erectile capability or sexual function following treatment [86]. In another study [97], no sexual dysfunction occurred in nineteen patients treated.

7.2.3 Sexual activity after glans resurfacing

In one study with ten patients [100], seven out of ten completed questionnaires (International Index of Erectile Function [IIEF-5] and a non-validated 9-item questionnaire) at their six-month follow-up visit. There was no erectile dysfunction according to the median IIEF-5 score of 24. All patients who were sexually active before treatment were active again within three to five months. According to the (non-validated) questionnaire, seven out of seven patients stated that the sensation at the tip of their penis was either no different or better after surgery and that they had erections within two to three weeks of surgery. Six out of seven patients had had sexual intercourse within three months of surgery and five out of seven patients felt that their sex life had improved. Overall patient satisfaction with glans resurfacing was high.

7.2.4 Sexual activity after glansectomy

Two studies reported sexual function after glansectomy [101, 102]. In one study (n = 68) with unclear methodology [102], 79% did not report any decline in spontaneous erection, rigidity and penetrative capacity after surgery, while 75% reported recovery of orgasm. In another study [103], all twelve patients had returned to 'normal' sexual activity one month after surgery.

7.2.5 **Sexual function after partial penectomy**

Sexual function after partial penectomy was reported by three studies [176-178]. The IIEF questionnaire was used in eighteen patients with a mean age of 52 years [176]. Post-operative scores were statistically worse for all domains of sexual function after partial penectomy. After surgery, 55.6% of patients had erectile function that allowed sexual intercourse. In patients who did not resume sexual intercourse after partial penectomy, 50% were ashamed of their small penis and missing glans, while another third blamed surgical complications. Of those who had resumed sexual intercourse, 66.7% reported the same frequency and level of sexual activity as before surgery, while 72.2% continued to have ejaculation and orgasm every time they had sexual activity. Overall, only 33.3% maintained their pre-operative frequency of sexual intercourse and were satisfied with their sex life.

An 'Overall Sexual Functioning Questionnaire' was used in fourteen out of eighteen patients with a median time since surgery of 11.5 months (range 6-72) [177]. Prior to surgery, all patients had normal erectile function and intercourse at least once a month. In nine out of fourteen patients, sexual functioning was 'normal' or 'slightly decreased', while three out of fourteen patients had no sexual intercourse after surgery. Alei *et al.* showed an improvement in erectile function over time [178].

7.2.6 **Quality of life after partial penectomy**

Several qualitative and quantitative instruments were used to assess 'psychological behaviour and adjustment' and 'social activity' as QoL indicators [177]. Patients reported fears of mutilation and of loss of sexual pleasure, as well as fear of dying and what this would mean for their families. Patients said family and partners were important in overcoming difficulties following surgery. The study reported no significant levels of anxiety and depression on the GHQ-12 (General Health Questionnaire) and HAD scale (Hospital Anxiety and Depression Scale), 'Social activity' remained the same after surgery in terms of living conditions, family life and social interactions.

7.3 **Total phallic reconstruction**

There is very limited data about total phallic reconstruction [119, 179, 180] following full- or near-total penile amputation. It is not possible to restore function. Cosmetically acceptable results are obtainable.

7.4 **Specialised care**

It is possible to cure almost 80% of penile cancer patients at all stages. Whenever possible, organ-preserving treatment should be offered [49] as it permits better QoL and sexual function than with partial penectomy. Patients should be referred to an experienced centre. Psychological support is very important for penile cancer patients.

8. REFERENCES

1. Hakenberg, O.W., *et al.* EAU guidelines on penile cancer: 2014 update. *Eur Urol*, 2015. 67: 142. <http://www.ncbi.nlm.nih.gov/pubmed/25457021>
2. Clark, P.E., *et al.* Penile cancer: Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*, 2013. 11: 594. <http://www.ncbi.nlm.nih.gov/pubmed/23667209>
3. Souillac, I., *et al.* [Penile cancer in 2010: update from the Oncology Committee of the French Association of Urology: external genital organs group (CCAFU-OGE)]. *Prog Urol*, 2011. 21: 909. <http://www.ncbi.nlm.nih.gov/pubmed/22118355>
4. Van Poppel, H., *et al.* Penile cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2013. 24 Suppl 6: vi115. <http://www.ncbi.nlm.nih.gov/pubmed/23975666>
5. Phillips B, *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998. <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009>
6. Robinson, R., *et al.* What are the risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy for penile cancer? 2015. PROSPERO CRD42015024904. https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015024904
7. Backes, D.M., *et al.* Systematic review of human papillomavirus prevalence in invasive penile cancer. *Cancer Causes Control*, 2009. 20: 449. <http://www.ncbi.nlm.nih.gov/pubmed/19082746>

8. Chaux, A., *et al.* Epidemiologic profile, sexual history, pathologic features, and human papillomavirus status of 103 patients with penile carcinoma. *World J Urol*, 2013. 31: 861.
<http://www.ncbi.nlm.nih.gov/pubmed/22116602>
9. Cancer Incidence in Five Continents Vol. VIII. IARC Scientific Publication No. 155. Vol. Vol III. 2002, The International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon CEDEX 08, France.
<http://www.iarc.fr/en/publications/pdfs-online/epi/sp155/>
10. Parkin, D.M., *et al.* Chapter 2: The burden of HPV-related cancers. *Vaccine*, 2006. 24 Suppl 3: S3/11.
<http://www.ncbi.nlm.nih.gov/pubmed/16949997>
11. Baldur-Felskov, B., *et al.* Increased incidence of penile cancer and high-grade penile intraepithelial neoplasia in Denmark 1978-2008: a nationwide population-based study. *Cancer Causes Control*, 2012. 23: 273.
<http://www.ncbi.nlm.nih.gov/pubmed/22101453>
12. Arya, M., *et al.* Long-term trends in incidence, survival and mortality of primary penile cancer in England. *Cancer Causes Control*, 2013. 24: 2169.
<http://www.ncbi.nlm.nih.gov/pubmed/24101363>
13. Barnholtz-Sloan, J.S., *et al.* Incidence trends in primary malignant penile cancer. *Urol Oncol*, 2007. 25: 361.
<http://www.ncbi.nlm.nih.gov/pubmed/17826651>
14. Dillner, J., *et al.* Etiology of squamous cell carcinoma of the penis. *Scand J Urol Nephrol Suppl*, 2000: 189.
<http://www.ncbi.nlm.nih.gov/pubmed/11144896>
15. Maden, C., *et al.* History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *J Natl Cancer Inst*, 1993. 85: 19.
<http://www.ncbi.nlm.nih.gov/pubmed/8380060>
16. Tsen, H.F., *et al.* Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). *Cancer Causes Control*, 2001. 12: 267.
<http://www.ncbi.nlm.nih.gov/pubmed/11405332>
17. Archier, E., *et al.* Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*, 2012. 26 Suppl 3: 22.
<http://www.ncbi.nlm.nih.gov/pubmed/22512677>
18. Stern, R.S. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *J Am Acad Dermatol*, 2012. 66: 553.
<http://www.ncbi.nlm.nih.gov/pubmed/22264671>
19. Daling, J.R., *et al.* Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol*, 1992. 135: 180.
<http://www.ncbi.nlm.nih.gov/pubmed/1311142>
20. Stankiewicz, E., *et al.* HPV infection and immunochemical detection of cell-cycle markers in verrucous carcinoma of the penis. *Mod Pathol*, 2009. 22: 1160.
<http://www.ncbi.nlm.nih.gov/pubmed/19465901>
21. Koifman, L., *et al.* Epidemiological aspects of penile cancer in Rio de Janeiro: evaluation of 230 cases. *Int Braz J Urol*, 2011. 37: 231.
<http://www.ncbi.nlm.nih.gov/pubmed/21557840>
22. Thuret, R., *et al.* A population-based analysis of the effect of marital status on overall and cancer-specific mortality in patients with squamous cell carcinoma of the penis. *Cancer Causes Control*, 2013. 24: 71.
<http://www.ncbi.nlm.nih.gov/pubmed/23109172>
23. McIntyre, M., *et al.* Penile cancer: an analysis of socioeconomic factors at a southeastern tertiary referral center. *Can J Urol*, 2011. 18: 5524.
<http://www.ncbi.nlm.nih.gov/pubmed/21333043>
24. Benard, V.B., *et al.* Examining the association between socioeconomic status and potential human papillomavirus-associated cancers. *Cancer*, 2008. 113: 2910.
<http://www.ncbi.nlm.nih.gov/pubmed/18980274>
25. Ulf-Moller, C.J., *et al.* Marriage, cohabitation and incidence trends of invasive penile squamous cell carcinoma in Denmark 1978-2010. *Int J Cancer*, 2013. 133: 1173.
<http://www.ncbi.nlm.nih.gov/pubmed/23404289>
26. Kayes, O., *et al.* Molecular and genetic pathways in penile cancer. *Lancet Oncol*, 2007. 8: 420.
<http://www.ncbi.nlm.nih.gov/pubmed/17466899>

27. Munoz, N., *et al.* Chapter 1: HPV in the etiology of human cancer. *Vaccine*, 2006. 24 Suppl 3: S3/1. <http://www.ncbi.nlm.nih.gov/pubmed/16949995>
28. Nordenvall, C., *et al.* Cancer risk among patients with condylomata acuminata. *Int J Cancer*, 2006. 119: 888. <http://www.ncbi.nlm.nih.gov/pubmed/16557590>
29. Lont, A.P., *et al.* Presence of high-risk human papillomavirus DNA in penile carcinoma predicts favorable outcome in survival. *Int J Cancer*, 2006. 119: 1078. <http://www.ncbi.nlm.nih.gov/pubmed/16570278>
30. Bezerra, A.L., *et al.* Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. *Cancer*, 2001. 91: 2315. <http://www.ncbi.nlm.nih.gov/pubmed/11413520>
31. Philippou, P., *et al.* Genital lichen sclerosus/balanitis xerotica obliterans in men with penile carcinoma: a critical analysis. *BJU Int*, 2013. 111: 970. <http://www.ncbi.nlm.nih.gov/pubmed/23356463>
32. D'Hauwers, K.W., *et al.* Human papillomavirus, lichen sclerosus and penile cancer: a study in Belgium. *Vaccine*, 2012. 30: 6573. <http://www.ncbi.nlm.nih.gov/pubmed/22939906>
33. Newman, P.A., *et al.* HPV vaccine acceptability among men: a systematic review and meta-analysis. *Sex Transm Infect*, 2013. 89: 568. <http://www.ncbi.nlm.nih.gov/pubmed/23828943>
34. Fisher, H., *et al.* Inequalities in the uptake of human papillomavirus vaccination: a systematic review and meta-analysis. *Int J Epidemiol*, 2013. 42: 896. <http://www.ncbi.nlm.nih.gov/pubmed/23620381>
35. Van Howe, R.S., *et al.* The carcinogenicity of smegma: debunking a myth. *J Eur Acad Dermatol Venereol*, 2006. 20: 1046. <http://www.ncbi.nlm.nih.gov/pubmed/16987256>
36. Daling, J.R., *et al.* Penile cancer: importance of circumcision, human papillomavirus and smoking in *in situ* and invasive disease. *Int J Cancer*, 2005. 116: 606. <http://www.ncbi.nlm.nih.gov/pubmed/15825185>
37. Velazquez, E.F., *et al.* Limitations in the interpretation of biopsies in patients with penile squamous cell carcinoma. *Int J Surg Pathol*, 2004. 12: 139. <http://www.ncbi.nlm.nih.gov/pubmed/15173919>
38. Velazquez, E.F., *et al.* Lichen sclerosus in 68 patients with squamous cell carcinoma of the penis: frequent atypias and correlation with special carcinoma variants suggests a precancerous role. *Am J Surg Pathol*, 2003. 27: 1448. <http://www.ncbi.nlm.nih.gov/pubmed/14576478>
39. Teichman, J.M., *et al.* Noninfectious penile lesions. *Am Fam Physician*, 2010. 81: 167. <http://www.ncbi.nlm.nih.gov/pubmed/20082512>
40. Renaud-Vilmer, C., *et al.* Analysis of alterations adjacent to invasive squamous cell carcinoma of the penis and their relationship with associated carcinoma. *J Am Acad Dermatol*, 2010. 62: 284. <http://www.ncbi.nlm.nih.gov/pubmed/20115951>
41. Cubilla, A.L., *et al.* Pathologic features of epidermoid carcinoma of the penis. A prospective study of 66 cases. *Am J Surg Pathol*, 1993. 17: 753. <http://www.ncbi.nlm.nih.gov/pubmed/8338190>
42. Chauv, A., *et al.* Papillary squamous cell carcinoma, not otherwise specified (NOS) of the penis: clinicopathologic features, differential diagnosis, and outcome of 35 cases. *Am J Surg Pathol*, 2010. 34: 223. <http://www.ncbi.nlm.nih.gov/pubmed/20061934>
43. Mannweiler, S., *et al.* Clear-cell differentiation and lymphatic invasion, but not the revised TNM classification, predict lymph node metastases in pT1 penile cancer: a clinicopathologic study of 76 patients from a low incidence area. *Urol Oncol*, 2013. 31: 1378. <http://www.ncbi.nlm.nih.gov/pubmed/22421354>
44. Gunia, S., *et al.* Inherent grading characteristics of individual pathologists contribute to clinically and prognostically relevant interobserver discordance concerning Broders' grading of penile squamous cell carcinomas. *Urol Int*, 2013. 90: 207. <http://www.ncbi.nlm.nih.gov/pubmed/23108244>
45. Oertell, J., *et al.* Differentiated precursor lesions and low-grade variants of squamous cell carcinomas are frequent findings in foreskins of patients from a region of high penile cancer incidence. *Histopathology*, 2011. 58: 925. <http://www.ncbi.nlm.nih.gov/pubmed/21585428>

46. Cubilla, A.L. The role of pathologic prognostic factors in squamous cell carcinoma of the penis. *World J Urol*, 2009. 27: 169.
<http://www.ncbi.nlm.nih.gov/pubmed/18766352>
47. Velazquez, E.F., *et al.* Epithelial abnormalities and precancerous lesions of anterior urethra in patients with penile carcinoma: a report of 89 cases. *Mod Pathol*, 2005. 18: 917.
<http://www.ncbi.nlm.nih.gov/pubmed/15920559>
48. Rees RW, F.A., Borley N, *et al.* pT2 penile squamous cell carcinomas: cavernosus vs. spongiosus invasion. *Eur Urol Suppl*, 2008. 7: 111 (abstract #163).
[http://www.europeanurology.com/article/S1569-9056\(08\)60162-1/fulltext](http://www.europeanurology.com/article/S1569-9056(08)60162-1/fulltext)
49. Leijte, J.A., *et al.* Evaluation of current TNM classification of penile carcinoma. *J Urol*, 2008. 180: 933.
<http://www.ncbi.nlm.nih.gov/pubmed/18635216>
50. Solsona, E., *et al.* Prospective validation of the association of local tumor stage and grade as a predictive factor for occult lymph node micrometastasis in patients with penile carcinoma and clinically negative inguinal lymph nodes. *J Urol*, 2001. 165: 1506.
<http://www.ncbi.nlm.nih.gov/pubmed/11342906>
51. Hungerhuber, E., *et al.* Risk stratification in penile carcinoma: 25-year experience with surgical inguinal lymph node staging. *Urology*, 2006. 68: 621.
<http://www.ncbi.nlm.nih.gov/pubmed/16979733>
52. Chau, A., *et al.* The prognostic index: a useful pathologic guide for prediction of nodal metastases and survival in penile squamous cell carcinoma. *Am J Surg Pathol*, 2009. 33: 1049.
<http://www.ncbi.nlm.nih.gov/pubmed/19384188>
53. Fromont, G., *et al.* 8q24 amplification is associated with Myc expression and prostate cancer progression and is an independent predictor of recurrence after radical prostatectomy. *Hum Pathol*, 2013. 44: 1617.
<http://www.ncbi.nlm.nih.gov/pubmed/23574779>
54. Alves, G., *et al.* Genetic imbalances in 26 cases of penile squamous cell carcinoma. *Genes Chromosomes Cancer*, 2001. 31: 48.
<http://www.ncbi.nlm.nih.gov/pubmed/11284035>
55. Alves, G., *et al.* Determination of telomerase activity in squamous cell carcinoma of the penis. *Int J Oncol*, 2001. 18: 67.
<http://www.ncbi.nlm.nih.gov/pubmed/11115540>
56. Kayes, O.J., *et al.* DNA replication licensing factors and aneuploidy are linked to tumor cell cycle state and clinical outcome in penile carcinoma. *Clin Cancer Res*, 2009. 15: 7335.
<http://www.ncbi.nlm.nih.gov/pubmed/19920109>
57. Gunia, S., *et al.* p16(INK4a) is a marker of good prognosis for primary invasive penile squamous cell carcinoma: a multi-institutional study. *J Urol*, 2012. 187: 899.
<http://www.ncbi.nlm.nih.gov/pubmed/22245329>
58. Poetsch, M., *et al.* Alterations in the tumor suppressor gene p16(INK4A) are associated with aggressive behavior of penile carcinomas. *Virchows Arch*, 2011. 458: 221.
<http://www.ncbi.nlm.nih.gov/pubmed/21085986>
59. Gunia, S., *et al.* Expression of p53, p21 and cyclin D1 in penile cancer: p53 predicts poor prognosis. *J Clin Pathol*, 2012. 65: 232.
<http://www.ncbi.nlm.nih.gov/pubmed/22135025>
60. Protzel, C., *et al.* Down-regulation of the metastasis suppressor protein KAI1/CD82 correlates with occurrence of metastasis, prognosis and presence of HPV DNA in human penile squamous cell carcinoma. *Virchows Arch*, 2008. 452: 369.
<http://www.ncbi.nlm.nih.gov/pubmed/18305955>
61. Velazquez, E.F., *et al.* Positive resection margins in partial penectomies: sites of involvement and proposal of local routes of spread of penile squamous cell carcinoma. *Am J Surg Pathol*, 2004. 28: 384.
<http://www.ncbi.nlm.nih.gov/pubmed/15104302>
62. Minhas, S., *et al.* What surgical resection margins are required to achieve oncological control in men with primary penile cancer? *BJU Int*, 2005. 96: 1040.
<http://www.ncbi.nlm.nih.gov/pubmed/16225525>
63. Brierley, JD., *et al.* TNM Classification of Malignant Tumours, 8th Edn. International Union Against Cancer, Wiley-Blackwell, 2016. pp. 188-9.
64. Bertolotto, M., *et al.* Primary and secondary malignancies of the penis: ultrasound features. *Abdom Imaging*, 2005. 30: 108.
<http://www.ncbi.nlm.nih.gov/pubmed/15759326>

65. Lont, A.P., *et al.* A comparison of physical examination and imaging in determining the extent of primary penile carcinoma. *BJU Int*, 2003. 91: 493.
<http://www.ncbi.nlm.nih.gov/pubmed/12656901>
66. Kayes, O., *et al.* The role of magnetic resonance imaging in the local staging of penile cancer. *Eur Urol*, 2007. 51: 1313.
<http://www.ncbi.nlm.nih.gov/pubmed/17113213>
67. Petralia, G., *et al.* Local staging of penile cancer using magnetic resonance imaging with pharmacologically induced penile erection. *Radiol Med*, 2008. 113: 517.
<http://www.ncbi.nlm.nih.gov/pubmed/18478188>
68. Krishna, R.P., *et al.* Sonography: an underutilized diagnostic tool in the assessment of metastatic groin nodes. *J Clin Ultrasound*, 2008. 36: 212.
<http://www.ncbi.nlm.nih.gov/pubmed/17960822>
69. Mueller-Lisse, U.G., *et al.* Functional imaging in penile cancer: PET/computed tomography, MRI, and sentinel lymph node biopsy. *Curr Opin Urol*, 2008. 18: 105.
<http://www.ncbi.nlm.nih.gov/pubmed/18090498>
70. Leijte, J.A., *et al.* Prospective evaluation of hybrid 18F-fluorodeoxyglucose positron emission tomography/computed tomography in staging clinically node-negative patients with penile carcinoma. *BJU Int*, 2009. 104: 640.
<http://www.ncbi.nlm.nih.gov/pubmed/19281465>
71. Schlenker, B., *et al.* Detection of inguinal lymph node involvement in penile squamous cell carcinoma by 18F-fluorodeoxyglucose PET/CT: a prospective single-center study. *Urol Oncol*, 2012. 30: 55.
<http://www.ncbi.nlm.nih.gov/pubmed/20022269>
72. Alkatout, I., *et al.* Squamous cell carcinoma of the penis: predicting nodal metastases by histologic grade, pattern of invasion and clinical examination. *Urol Oncol*, 2011. 29: 774.
<http://www.ncbi.nlm.nih.gov/pubmed/20060332>
73. Graafland, N.M., *et al.* Prognostic factors for occult inguinal lymph node involvement in penile carcinoma and assessment of the high-risk EAU subgroup: a two-institution analysis of 342 clinically node-negative patients. *Eur Urol*, 2010. 58: 742.
<http://www.ncbi.nlm.nih.gov/pubmed/20800339>
74. Souillac, I., *et al.* Prospective evaluation of (18)F-fluorodeoxyglucose positron emission tomography-computerized tomography to assess inguinal lymph node status in invasive squamous cell carcinoma of the penis. *J Urol*, 2012. 187: 493.
<http://www.ncbi.nlm.nih.gov/pubmed/22177157>
75. Horenblas, S., *et al.* Squamous cell carcinoma of the penis. III. Treatment of regional lymph nodes. *J Urol*, 1993. 149: 492.
<http://www.ncbi.nlm.nih.gov/pubmed/8437253>
76. Ornellas, A.A., *et al.* Surgical treatment of invasive squamous cell carcinoma of the penis: retrospective analysis of 350 cases. *J Urol*, 1994. 151: 1244.
<http://www.ncbi.nlm.nih.gov/pubmed/7512656>
77. Zhu, Y., *et al.* Predicting pelvic lymph node metastases in penile cancer patients: a comparison of computed tomography, Cloquet's node, and disease burden of inguinal lymph nodes. *Onkologie*, 2008. 31: 37.
<http://www.ncbi.nlm.nih.gov/pubmed/18268397>
78. Graafland, N.M., *et al.* Scanning with 18F-FDG-PET/CT for detection of pelvic nodal involvement in inguinal node-positive penile carcinoma. *Eur Urol*, 2009. 56: 339.
<http://www.ncbi.nlm.nih.gov/pubmed/19477581>
79. Zhu, Y., *et al.* The value of squamous cell carcinoma antigen in the prognostic evaluation, treatment monitoring and followup of patients with penile cancer. *J Urol*, 2008. 180: 2019.
<http://www.ncbi.nlm.nih.gov/pubmed/18801542>
80. Leijte, J.A., *et al.* Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. *Eur Urol*, 2008. 54: 161.
<http://www.ncbi.nlm.nih.gov/pubmed/18440124>
81. Alnajjar, H.M., *et al.* Treatment of carcinoma *in situ* of the glans penis with topical chemotherapy agents. *Eur Urol*, 2012. 62: 923.
<http://www.ncbi.nlm.nih.gov/pubmed/22421082>
82. Paoli, J., *et al.* Penile intraepithelial neoplasia: results of photodynamic therapy. *Acta Derm Venereol*, 2006. 86: 418.
<http://www.ncbi.nlm.nih.gov/pubmed/16955186>

83. Shabbir, M., *et al.* Glans resurfacing for the treatment of carcinoma *in situ* of the penis: surgical technique and outcomes. *Eur Urol*, 2011. 59: 142.
<http://www.ncbi.nlm.nih.gov/pubmed/21050658>
84. Philippou, P., *et al.* Conservative surgery for squamous cell carcinoma of the penis: resection margins and long-term oncological control. *J Urol*, 2012. 188: 803.
<http://www.ncbi.nlm.nih.gov/pubmed/22818137>
85. Ornellas, A.A., *et al.* Surgical treatment of invasive squamous cell carcinoma of the penis: Brazilian National Cancer Institute long-term experience. *J Surg Oncol*, 2008. 97: 487.
<http://www.ncbi.nlm.nih.gov/pubmed/18425779>
86. Bandieramonte, G., *et al.* Peniscopically controlled CO2 laser excision for conservative treatment of *in situ* and T1 penile carcinoma: report on 224 patients. *Eur Urol*, 2008. 54: 875.
<http://www.ncbi.nlm.nih.gov/pubmed/18243513>
87. Colecchia, M., *et al.* pT1 penile squamous cell carcinoma: a clinicopathologic study of 56 cases treated by CO2 laser therapy. *Anal Quant Cytol Histol*, 2009. 31: 153.
<http://www.ncbi.nlm.nih.gov/pubmed/19639702>
88. Piva, L., *et al.* [Therapeutic alternatives in the treatment of class T1N0 squamous cell carcinoma of the penis: indications and limitations]. *Arch Ital Urol Androl*, 1996. 68: 157.
<http://www.ncbi.nlm.nih.gov/pubmed/8767503>
89. Frimberger, D., *et al.* Penile carcinoma. Is Nd:YAG laser therapy radical enough? *J Urol*, 2002. 168: 2418.
<http://www.ncbi.nlm.nih.gov/pubmed/12441930>
90. Meijer, R.P., *et al.* Long-term follow-up after laser therapy for penile carcinoma. *Urology*, 2007. 69: 759.
<http://www.ncbi.nlm.nih.gov/pubmed/17445665>
91. Rothenberger, K.H., *et al.* [Laser therapy of penile carcinoma]. *Urologe A*, 1994. 33: 291.
<http://www.ncbi.nlm.nih.gov/pubmed/7941174>
92. Schlenker, B., *et al.* Organ-preserving neodymium-yttrium-aluminium-garnet laser therapy for penile carcinoma: a long-term follow-up. *BJU Int*, 2010. 106: 786.
<http://www.ncbi.nlm.nih.gov/pubmed/20089106>
93. Schlenker, B., *et al.* Intermediate-differentiated invasive (pT1 G2) penile cancer--oncological outcome and follow-up. *Urol Oncol*, 2011. 29: 782.
<http://www.ncbi.nlm.nih.gov/pubmed/19945307>
94. Skeppner, E., *et al.* Treatment-seeking, aspects of sexual activity and life satisfaction in men with laser-treated penile carcinoma. *Eur Urol*, 2008. 54: 631.
<http://www.ncbi.nlm.nih.gov/pubmed/18788122>
95. Windahl, T., *et al.* Combined laser treatment for penile carcinoma: results after long-term followup. *J Urol*, 2003. 169: 2118.
<http://www.ncbi.nlm.nih.gov/pubmed/12771731>
96. Tietjen, D.N., *et al.* Laser therapy of squamous cell dysplasia and carcinoma of the penis. *Urology*, 1998. 52: 559.
<http://www.ncbi.nlm.nih.gov/pubmed/9763071>
97. van Bezooijen, B.P., *et al.* Laser therapy for carcinoma *in situ* of the penis. *J Urol*, 2001. 166: 1670.
<http://www.ncbi.nlm.nih.gov/pubmed/11586199>
98. Mohs, F.E., *et al.* Mohs micrographic surgery for penile tumors. *Urol Clin North Am*, 1992. 19: 291.
<http://www.ncbi.nlm.nih.gov/pubmed/1574820>
99. Shindel, A.W., *et al.* Mohs micrographic surgery for penile cancer: management and long-term followup. *J Urol*, 2007. 178: 1980.
<http://www.ncbi.nlm.nih.gov/pubmed/17869306>
100. Hadway, P., *et al.* Total glans resurfacing for premalignant lesions of the penis: initial outcome data. *BJU Int*, 2006. 98: 532.
<http://www.ncbi.nlm.nih.gov/pubmed/16925748>
101. Ayres, B., *et al.*, Glans resurfacing – a new penile preserving option for superficially invasive penile cancer. 2010.
102. Austoni E, G.A., *et al.*, Reconstructive surgery for penile cancer with preservation of sexual function. *Eur Urol Suppl*, 2008. 7: 116 (Abstract #183).
103. Li, J., *et al.* Organ-sparing surgery for penile cancer: complications and outcomes. *Urology*, 2011. 78: 1121.
<http://www.ncbi.nlm.nih.gov/pubmed/22054385>

104. Smith, Y., *et al.* Reconstructive surgery for invasive squamous carcinoma of the glans penis. *Eur Urol*, 2007. 52: 1179.
<http://www.ncbi.nlm.nih.gov/pubmed/17349734>
105. Morelli, G., *et al.* Glansectomy with split-thickness skin graft for the treatment of penile carcinoma. *Int J Impot Res*, 2009. 21: 311.
<http://www.ncbi.nlm.nih.gov/pubmed/19458620>
106. Khezri, A.A., *et al.* Carcinoma of the penis. *Br J Urol*, 1978. 50: 275.
<http://www.ncbi.nlm.nih.gov/pubmed/753475>
107. Modig, H., *et al.* Carcinoma of the penis. Treatment by surgery or combined bleomycin and radiation therapy. *Acta Oncol*, 1993. 32: 653.
<http://www.ncbi.nlm.nih.gov/pubmed/7505090>
108. Persky, L., *et al.* Carcinoma of the penis. *CA Cancer J Clin*, 1986. 36: 258.
<http://www.ncbi.nlm.nih.gov/pubmed/3093013>
109. Lummen, G., *et al.* [Treatment and follow-up of patients with squamous epithelial carcinoma of the penis]. *Urologe A*, 1997. 36: 157.
<http://www.ncbi.nlm.nih.gov/pubmed/9199044>
110. Crook, J., *et al.*, MP-21.03: Penile brachytherapy: results for 60 patients. *Urology*, 2007. 70: 161.
111. Crook, J., *et al.* Penile brachytherapy: technical aspects and postimplant issues. *Brachytherapy*, 2010. 9: 151.
<http://www.ncbi.nlm.nih.gov/pubmed/19854685>
112. Crook, J., *et al.* Radiation therapy in the management of the primary penile tumor: an update. *World J Urol*, 2009. 27: 189.
<http://www.ncbi.nlm.nih.gov/pubmed/18636264>
113. de Crevoisier, R., *et al.* Long-term results of brachytherapy for carcinoma of the penis confined to the glans (N- or NX). *Int J Radiat Oncol Biol Phys*, 2009. 74: 1150.
<http://www.ncbi.nlm.nih.gov/pubmed/19395183>
114. Gotsadze, D., *et al.* Is conservative organ-sparing treatment of penile carcinoma justified? *Eur Urol*, 2000. 38: 306.
<http://www.ncbi.nlm.nih.gov/pubmed/10940705>
115. Ozsahin, M., *et al.* Treatment of penile carcinoma: to cut or not to cut? *Int J Radiat Oncol Biol Phys*, 2006. 66: 674.
<http://www.ncbi.nlm.nih.gov/pubmed/16949770>
116. Crook, J.M., *et al.* American Brachytherapy Society-Groupe Europeen de Curietherapie-European Society of Therapeutic Radiation Oncology (ABS-GEC-ESTRO) consensus statement for penile brachytherapy. *Brachytherapy*, 2013. 12: 191.
<http://www.ncbi.nlm.nih.gov/pubmed/23453681>
117. Azrif, M., *et al.* External-beam radiotherapy in T1-2 N0 penile carcinoma. *Clin Oncol (R Coll Radiol)*, 2006. 18: 320.
<http://www.ncbi.nlm.nih.gov/pubmed/16703750>
118. Zouhair, A., *et al.* Radiation therapy alone or combined surgery and radiation therapy in squamous-cell carcinoma of the penis? *Eur J Cancer*, 2001. 37: 198.
<http://www.ncbi.nlm.nih.gov/pubmed/11166146>
119. Garaffa, G., *et al.* Total phallic reconstruction after penile amputation for carcinoma. *BJU Int*, 2009. 104: 852.
<http://www.ncbi.nlm.nih.gov/pubmed/19239449>
120. Salgado, C.J., *et al.* Glans penis coronoplasty with palmaris longus tendon following total penile reconstruction. *Ann Plast Surg*, 2009. 62: 690.
<http://www.ncbi.nlm.nih.gov/pubmed/19461287>
121. Saisorn, I., *et al.* Fine-needle aspiration cytology predicts inguinal lymph node metastasis without antibiotic pretreatment in penile carcinoma. *BJU Int*, 2006. 97: 1225.
<http://www.ncbi.nlm.nih.gov/pubmed/16686716>
122. Rosevear, H.M., *et al.* Utility of (1)(8)F-FDG PET/CT in identifying penile squamous cell carcinoma metastatic lymph nodes. *Urol Oncol*, 2012. 30: 723.
<http://www.ncbi.nlm.nih.gov/pubmed/21396850>
123. Horenblas, S. Lymphadenectomy for squamous cell carcinoma of the penis. Part 1: diagnosis of lymph node metastasis. *BJU Int*, 2001. 88: 467.
<http://www.ncbi.nlm.nih.gov/pubmed/11589659>
124. Stuijver, M.M., *et al.* Early wound complications after inguinal lymphadenectomy in penile cancer: a historical cohort study and risk-factor analysis. *Eur Urol*, 2013. 64: 486.
<http://www.ncbi.nlm.nih.gov/pubmed/23490726>

125. Koifman, L., *et al.* Radical open inguinal lymphadenectomy for penile carcinoma: surgical technique, early complications and late outcomes. *J Urol*, 2013. 190: 2086.
<http://www.ncbi.nlm.nih.gov/pubmed/23770135>
126. Yao, K., *et al.* Modified technique of radical inguinal lymphadenectomy for penile carcinoma: morbidity and outcome. *J Urol*, 2010. 184: 546.
<http://www.ncbi.nlm.nih.gov/pubmed/20620415>
127. Hegarty, P.K., *et al.* Controversies in ilioinguinal lymphadenectomy. *Urol Clin North Am*, 2010. 37: 421.
<http://www.ncbi.nlm.nih.gov/pubmed/20674697>
128. Lughezzani, G., *et al.* The Relationship Between Lymph Node Ratio and Cancer-Specific Survival in a Contemporary Series of Patients with Penile Cancer and Lymph Node Metastases. *BJU Int*, 2013. 116: 727.
<http://www.ncbi.nlm.nih.gov/pubmed/24128128>
129. Protzel, C., *et al.* Lymphadenectomy in the surgical management of penile cancer. *Eur Urol*, 2009. 55: 1075.
<http://www.ncbi.nlm.nih.gov/pubmed/19264390>
130. Thuret, R., *et al.* A contemporary population-based assessment of the rate of lymph node dissection for penile carcinoma. *Ann Surg Oncol*, 2011. 18: 439.
<http://www.ncbi.nlm.nih.gov/pubmed/20839061>
131. La-Touche, S., *et al.* Trial of ligation versus coagulation of lymphatics in dynamic inguinal sentinel lymph node biopsy for staging of squamous cell carcinoma of the penis. *Ann R Coll Surg Engl*, 2012. 94: 344.
<http://www.ncbi.nlm.nih.gov/pubmed/22943231>
132. Tauber, R., *et al.* Inguinal lymph node dissection: epidermal vacuum therapy for prevention of wound complications. *J Plast Reconstr Aesthet Surg*, 2013. 66: 390.
<http://www.ncbi.nlm.nih.gov/pubmed/23107617>
133. Pahwa, H.S., *et al.* Video Endoscopic Inguinal Lymphadenectomy (VEIL)--a prospective critical perioperative assessment of feasibility and morbidity with points of technique in penile carcinoma. *World J Surg Oncol*, 2013. 11: 42.
<http://www.ncbi.nlm.nih.gov/pubmed/23432959>
134. Zhou, X.L., *et al.* Endoscopic inguinal lymphadenectomy for penile carcinoma and genital malignancy: a preliminary report. *J Endourol*, 2013. 27: 657.
<http://www.ncbi.nlm.nih.gov/pubmed/23268699>
135. Matin, S.F., *et al.* Phase 1 prospective evaluation of the oncological adequacy of robotic assisted video-endoscopic inguinal lymphadenectomy in patients with penile carcinoma. *BJU Int*, 2013. 111: 1068.
<http://www.ncbi.nlm.nih.gov/pubmed/23551693>
136. Tobias-Machado, M., *et al.* Video endoscopic inguinal lymphadenectomy: a new minimally invasive procedure for radical management of inguinal nodes in patients with penile squamous cell carcinoma. *J Urol*, 2007. 177: 953.
<http://www.ncbi.nlm.nih.gov/pubmed/17296386>
137. Cabanas, R.M. An approach for the treatment of penile carcinoma. *Cancer*, 1977. 39: 456.
<http://www.ncbi.nlm.nih.gov/pubmed/837331>
138. Lughezzani, G., *et al.* The relationship between characteristics of inguinal lymph nodes and pelvic lymph node involvement in penile squamous cell carcinoma: a single institution experience. *J Urol*, 2014. 191: 977.
<http://www.ncbi.nlm.nih.gov/pubmed/24262497>
139. Graafland, N.M., *et al.* Prognostic significance of extranodal extension in patients with pathological node positive penile carcinoma. *J Urol*, 2010. 184: 1347.
<http://www.ncbi.nlm.nih.gov/pubmed/20723934>
140. Lucky, M.A., *et al.* Referrals into a dedicated British penile cancer centre and sources of possible delay. *Sex Transm Infect*, 2009. 85: 527.
<http://www.ncbi.nlm.nih.gov/pubmed/19584061>
141. Pizzocaro, G., *et al.* Adjuvant and neoadjuvant vincristine, bleomycin, and methotrexate for inguinal metastases from squamous cell carcinoma of the penis. *Acta Oncol*, 1988. 27: 823.
<http://www.ncbi.nlm.nih.gov/pubmed/2466471>
142. Leijte, J.A., *et al.* Neoadjuvant chemotherapy in advanced penile carcinoma. *Eur Urol*, 2007. 52: 488.
<http://www.ncbi.nlm.nih.gov/pubmed/17316964>

143. Bermejo, C., *et al.* Neoadjuvant chemotherapy followed by aggressive surgical consolidation for metastatic penile squamous cell carcinoma. *J Urol*, 2007. 177: 1335.
<http://www.ncbi.nlm.nih.gov/pubmed/17382727>
144. Pizzocaro, G., *et al.* Taxanes in combination with cisplatin and fluorouracil for advanced penile cancer: preliminary results. *Eur Urol*, 2009. 55: 546.
<http://www.ncbi.nlm.nih.gov/pubmed/18649992>
145. Graafland, N.M., *et al.* Inguinal recurrence following therapeutic lymphadenectomy for node positive penile carcinoma: outcome and implications for management. *J Urol*, 2011. 185: 888.
<http://www.ncbi.nlm.nih.gov/pubmed/21239009>
146. Kulkarni, J.N., *et al.* Prophylactic bilateral groin node dissection versus prophylactic radiotherapy and surveillance in patients with N0 and N1-2A carcinoma of the penis. *Eur Urol*, 1994. 26: 123.
<http://www.ncbi.nlm.nih.gov/pubmed/7957466>
147. Franks, K.N., *et al.* Radiotherapy for node positive penile cancer: experience of the Leeds teaching hospitals. *J Urol*, 2011. 186: 524.
<http://www.ncbi.nlm.nih.gov/pubmed/21700296>
148. Burt, L.M., *et al.* Stage presentation, care patterns, and treatment outcomes for squamous cell carcinoma of the penis. *Int J Radiat Oncol Biol Phys*, 2014. 88: 94.
<http://www.ncbi.nlm.nih.gov/pubmed/24119832>
149. Sonpavde, G., *et al.* Penile cancer: current therapy and future directions. *Ann Oncol*, 2013. 24: 1179.
<http://www.ncbi.nlm.nih.gov/pubmed/23293117>
150. Maiche, A.G. Adjuvant treatment using bleomycin in squamous cell carcinoma of penis: study of 19 cases. *Br J Urol*, 1983. 55: 542.
<http://www.ncbi.nlm.nih.gov/pubmed/6194844>
151. Pizzocaro, G., *et al.* Up-to-date management of carcinoma of the penis. *Eur Urol*, 1997. 32: 5.
<http://www.ncbi.nlm.nih.gov/pubmed/9266225>
152. Giannatempo P., *et al.* Survival analyses of adjuvant or neoadjuvant combination of a taxane plus cisplatin and 5-fluorouracil (T-PF) in patients with bulky nodal metastases from squamous cell carcinoma of the penis (PSCC): Results of a single high-volume center. *J Clin Oncol*, 2014. 32: 5.
<http://meetinglibrary.asco.org/content/124205-142>
153. Noronha, V., *et al.* Role of paclitaxel and platinum-based adjuvant chemotherapy in high-risk penile cancer. *Urol Ann*, 2012. 4: 150.
<http://www.ncbi.nlm.nih.gov/pubmed/23248520>
154. Hakenberg, O.W., *et al.* Cisplatin, methotrexate and bleomycin for treating advanced penile carcinoma. *BJU Int*, 2006. 98: 1225.
<http://www.ncbi.nlm.nih.gov/pubmed/17125480>
155. Haas, G.P., *et al.* Cisplatin, methotrexate and bleomycin for the treatment of carcinoma of the penis: a Southwest Oncology Group study. *J Urol*, 1999. 161: 1823.
<http://www.ncbi.nlm.nih.gov/pubmed/10332445>
156. Hussein, A.M., *et al.* Chemotherapy with cisplatin and 5-fluorouracil for penile and urethral squamous cell carcinomas. *Cancer*, 1990. 65: 433.
<http://www.ncbi.nlm.nih.gov/pubmed/2297633>
157. Shammas, F.V., *et al.* Cisplatin and 5-fluorouracil in advanced cancer of the penis. *J Urol*, 1992. 147: 630.
<http://www.ncbi.nlm.nih.gov/pubmed/1538445>
158. Theodore, C., *et al.* A phase II multicentre study of irinotecan (CPT 11) in combination with cisplatin (CDDP) in metastatic or locally advanced penile carcinoma (EORTC PROTOCOL 30992). *Ann Oncol*, 2008. 19: 1304.
<http://www.ncbi.nlm.nih.gov/pubmed/18417462>
159. Pagliaro, L.C., *et al.* Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. *J Clin Oncol*, 2010. 28: 3851.
<http://www.ncbi.nlm.nih.gov/pubmed/20625118>
160. Nicholson, S., *et al.* Phase II trial of docetaxel, cisplatin and 5FU chemotherapy in locally advanced and metastatic penis cancer (CRUK/09/001). *Br J Cancer*, 2013. 109: 2554.
<http://www.ncbi.nlm.nih.gov/pubmed/24169355>
161. Eliason, M., *et al.* Primary treatment of verrucous carcinoma of the penis with fluorouracil, cis-diamino-dichloro-platinum, and radiation therapy. *Arch Dermatol*, 2009. 145: 950.
<http://www.ncbi.nlm.nih.gov/pubmed/19687438>

162. Pond, G.R., *et al.* Prognostic risk stratification derived from individual patient level data for men with advanced penile squamous cell carcinoma receiving first-line systemic therapy. *Urol Oncol*, 2014. 32: 501.
<http://www.ncbi.nlm.nih.gov/pubmed/24332646>
163. Di Lorenzo, G., *et al.* Cisplatin and 5-fluorouracil in inoperable, stage IV squamous cell carcinoma of the penis. *BJU Int*, 2012. 110: E661.
<http://www.ncbi.nlm.nih.gov/pubmed/22958571>
164. Di Lorenzo, G., *et al.* Paclitaxel in pretreated metastatic penile cancer: final results of a phase 2 study. *Eur Urol*, 2011. 60: 1280.
<http://www.ncbi.nlm.nih.gov/pubmed/21871710>
165. Power, D.G., *et al.* Cisplatin and gemcitabine in the management of metastatic penile cancer. *Urol Oncol*, 2009. 27: 187.
<http://www.ncbi.nlm.nih.gov/pubmed/18367122>
166. Gou, H.F., *et al.* Epidermal growth factor receptor (EGFR)-RAS signaling pathway in penile squamous cell carcinoma. *PLoS One*, 2013. 8: e62175.
<http://www.ncbi.nlm.nih.gov/pubmed/23637996>
167. Necchi, A., *et al.* Proof of activity of anti-epidermal growth factor receptor-targeted therapy for relapsed squamous cell carcinoma of the penis. *J Clin Oncol*, 2011. 29: e650.
<http://www.ncbi.nlm.nih.gov/pubmed/21632506>
168. Carthon, B.C., *et al.* Epidermal growth factor receptor-targeted therapy in locally advanced or metastatic squamous cell carcinoma of the penis. *BJU Int*, 2014. 113: 871.
<http://www.ncbi.nlm.nih.gov/pubmed/24053151>
169. Zhu, Y., *et al.* Feasibility and activity of sorafenib and sunitinib in advanced penile cancer: a preliminary report. *Urol Int*, 2010. 85: 334.
<http://www.ncbi.nlm.nih.gov/pubmed/20980789>
170. Kroon, B.K., *et al.* Patients with penile carcinoma benefit from immediate resection of clinically occult lymph node metastases. *J Urol*, 2005. 173: 816.
<http://www.ncbi.nlm.nih.gov/pubmed/15711276>
171. Horenblas, S., *et al.* Local recurrent tumour after penis-conserving therapy. A plea for long-term follow-up. *Br J Urol*, 1993. 72: 976.
<http://www.ncbi.nlm.nih.gov/pubmed/8306171>
172. Djajadiningrat, R.S., *et al.* Penile Sparing Surgery for Penile Cancer-Does it Affect Survival? *J Urol*, 2013.
<http://www.ncbi.nlm.nih.gov/pubmed/24373799>
173. Kroon, B.K., *et al.* Ultrasonography-guided fine-needle aspiration cytology before sentinel node biopsy in patients with penile carcinoma. *BJU Int*, 2005. 95: 517.
<http://www.ncbi.nlm.nih.gov/pubmed/15705071>
174. Djajadiningrat, R.S., *et al.* Ultrasound examination and fine needle aspiration cytology-useful for followup of the regional nodes in penile cancer? *J Urol*, 2014. 191: 652.
<http://www.ncbi.nlm.nih.gov/pubmed/23994372>
175. Schover, L.R. Sexuality and fertility after cancer. *Hematology Am Soc Hematol Educ Program*, 2005: 523.
<http://www.ncbi.nlm.nih.gov/pubmed/16304430>
176. Romero, F.R., *et al.* Sexual function after partial penectomy for penile cancer. *Urology*, 2005. 66: 1292.
<http://www.ncbi.nlm.nih.gov/pubmed/16360459>
177. D'Ancona, C.A., *et al.* Quality of life after partial penectomy for penile carcinoma. *Urology*, 1997. 50: 593.
<http://www.ncbi.nlm.nih.gov/pubmed/9338738>
178. Alei, G., *et al.* Lichen sclerosus in patients with squamous cell carcinoma. Our experience with partial penectomy and reconstruction with ventral fenestrated flap. *Ann Ital Chir*, 2012. 83: 363.
<http://www.ncbi.nlm.nih.gov/pubmed/22759475>
179. Gerullis, H., *et al.* Construction of a penoid after penectomy using a transpositioned testicle. *Urol Int*, 2013. 90: 240.
<http://www.ncbi.nlm.nih.gov/pubmed/22922734>
180. Hage, J.J. Simple, safe, and satisfactory secondary penile enhancement after near-total oncologic amputation. *Ann Plast Surg*, 2009. 62: 685.
<http://www.ncbi.nlm.nih.gov/pubmed/19461286>

9. CONFLICT OF INTEREST

All members of the Penile Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <http://uroweb.org/guideline/penile-cancer/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a nonprofit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.



EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)

S. Gravas (Chair), T. Bach, M. Drake, M. Gacci, C. Gratzke,
T.R.W. Herrmann, S. Madersbacher, C. Mamoulakis,
K.A.O. Tikkinen

Guidelines Associates: M. Karavitis, S. Malde, V. Sakkalis,
R. Umbach

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1. INTRODUCTION

1.1 Aim and objectives

Lower urinary tract symptoms (LUTS) are a common complaint in adult men with a major impact on quality of life (QoL), and substantial economic burden. The present Guidelines offer practical evidence-based guidance on the assessment and treatment of men aged 40 years or older with various non-neurogenic benign forms of LUTS. The understanding of the LUT as a functional unit, and the multifactorial aetiology of associated symptoms, means that LUTS now constitute the main focus, rather than the former emphasis on Benign Prostatic Hyperplasia (BPH). It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Non-neurogenic Male LUTS Guidelines Panel consists of an international group of experts with urological and clinical epidemiological backgrounds. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/>.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: <http://www.uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/>.

1.4 Publication history

The Non-neurogenic Male LUTS Guidelines were first published in 2000. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. The 2017 document presents a comprehensive update of the 2016 publication. The literature was assessed for all chapters.

2. METHODS

2.1 Introduction

For the 2017 Management of Non-Neurogenic Male LUTS Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Non-Neurogenic Male LUTS Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies, published in the English language. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between April 1st 2015 and May 31st 2016. A total of 1,622 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <http://www.uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/supplementary-material>.

References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [1]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://www.uroweb.org/guidelines/>. A list of all Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The Non-Neurogenic Male LUTS Guidelines were peer reviewed prior to publication in 2016.

2.3 Patients to whom the guidelines apply

Recommendations apply to men aged 40 years or older who seek professional help for LUTS in various

non-neurogenic and non-malignant conditions such as LUTS/Benign Prostatic Obstruction (BPO), detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria. Men with other contexts of LUT disease (e.g. concomitant neurological diseases, young age, prior LUT disease or surgery) usually require a more extensive work-up, which is not covered in these Guidelines, but may include several tests mentioned in the following sections. EAU Guidelines on Neuro-Urology, Urinary Incontinence, Urological Infections, Urolithiasis, or malignant diseases of the LUT have been developed by other EAU Guidelines Panels and are available online: www.uroweb.org/guidelines/.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

Lower urinary tract symptoms can be divided into storage, voiding and post-micturition symptoms [2]. Lower urinary tract symptoms are prevalent, cause bother and impair QoL [3-6]. An increasing awareness of LUTS and storage symptoms in particular, is warranted to discuss management options that could increase QoL [7]. Lower urinary tract symptoms are strongly associated with ageing [3, 4], associated costs and burden are therefore likely to increase with future demographic changes [4, 8]. Lower urinary tract symptoms are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g. metabolic syndrome) [9]. Most elderly men have at least one LUTS [4], however, symptoms are often mild or not very bothersome [6, 7, 10]. Lower urinary tract symptoms progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [4]. LUTS have traditionally been related to bladder outlet obstruction (BOO), which is often caused by benign prostatic enlargement (BPE) resulting from the histologic condition of BPH [2, 5]. However, recent studies have shown that LUTS are often unrelated to the prostate [4, 11]. Bladder dysfunction may also cause LUTS, including detrusor overactivity/OAB, detrusor underactivity/underactive bladder, as well as other structural or functional abnormalities of the urinary tract and its surrounding tissues [11]. Prostatic inflammation also appears to play a role in BPH pathogenesis and progression [12, 13]. In addition, many non-urological conditions also contribute to urinary symptoms, especially nocturia [4].

The definitions of the most common conditions related to male LUTS are presented below:

- Acute retention of urine is defined as a painful, palpable or percussible bladder, when the patient is unable to pass any urine [2];
- Chronic retention of urine is defined as a non-painful bladder, which remains palpable or percussible after the patient has passed urine. Such patients may be incontinent [2];
- Bladder outlet obstruction is the generic term for obstruction during voiding and is characterised by increasing detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow-rate and detrusor pressure [2];
- Benign prostatic obstruction is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPE [2]. In the Guidelines either the term BPO or BOO is used as reported by the original studies;
- Benign prostatic hyperplasia is a term used (and reserved) for the typical histological pattern, which defines the disease;
- Detrusor overactivity (DO) is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [2];
- Overactive bladder syndrome is characterised by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [14].

Figure 1 illustrates the potential causes of LUTS. In any man complaining of LUTS, it is common for more than one of these factors to be present.

Figure 1: Causes of male lower urinary tract symptoms (LUTS)



4. DIAGNOSTIC EVALUATION

Tests are useful for diagnosis, monitoring, assessing the risk of disease progression, treatment planning, and the prediction of treatment outcomes. The clinical assessment of patients with LUTS has two main objectives:

- to identify the differential diagnoses, since the origin of male LUTS is multifactorial, the relevant EAU Guidelines on the management of applicable conditions should be followed in these cases;
- to define the clinical profile (including the risk of disease progression) of men with LUTS in order to provide appropriate care.

4.1 Medical history

The importance of assessing the patient's history is well recognised [15-17]. A medical history aims to identify the potential causes and relevant comorbidities, including medical and neurological diseases. In addition, current medication, lifestyle habits, emotional and psychological factors must be reviewed. The Panel recognises the need to discuss LUTS and the therapeutic pathway from the patient's perspective. This includes reassuring the patient that there is no definite link between LUTS and prostate cancer (PCa) [18, 19].

As part of the urological/surgical history, a self-completed validated symptom questionnaire (see section 4.2) should be obtained to objectify and quantify LUTS. Voiding diaries are particularly beneficial when assessing patients with nocturia and/or storage symptoms (see section 4.3). When relevant, sexual function should be assessed, preferably with validated symptom questionnaires such as the International Index for Erectile Function (IIEF).

Recommendation	LE	GR
Take a complete medical history from men with LUTS.	4	A*

*Upgraded based on Panel consensus.

4.2 Symptom score questionnaires

All published guidelines for male LUTS/BPH recommend using validated symptom score questionnaires [15, 17]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [20-26]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant, yet they are not disease-, or age-specific. A systematic review evaluating the diagnostic accuracy of individual symptoms and questionnaires, compared with urodynamic studies (the reference standard) for the diagnosis of BOO in males with LUTS found that individual symptoms and questionnaires for diagnosing BOO were not significantly associated with one another [27].

4.2.1 *The International Prostate Symptom Score (IPSS)*

The IPSS is an 8-item questionnaire, consisting of seven symptom questions and one QoL question [21]. The IPSS score is categorised as ‘asymptomatic’ (0 points), ‘mildly symptomatic’ (1-7 points), ‘moderately symptomatic’ (8-19 points), and ‘severely symptomatic’ (20-35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms, and bother caused by each separate symptom.

4.2.2 *The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)*

The ICIQ-MLUTS was created from the ICS Male questionnaire. It is a widely used and validated patient completed questionnaire [22]. It contains 13 items, with subscales for nocturia and OAB, and is available in 17 languages.

4.2.3 *Danish Prostate Symptom Score (DAN-PSS)*

The DAN-PSS [25] is a symptom score used mainly in Denmark and Finland. The ICIQ-MLUTS and DAN-PSS measure the bother of each individual LUTS.

Recommendation	LE	GR
Use a validated symptom score questionnaire including quality of life assessment during the assessment of male LUTS and for re-evaluation during and/or after treatment.	3	B

4.3 Frequency volume charts and bladder diaries

The recording of volume and time of each void by the patient is referred to as a frequency volume chart (FVC). Inclusion of additional information such as fluid intake, use of pads, activities during recording, or symptom scores is termed a bladder diary [2]. Parameters that can be derived from the FVC and bladder diary include: daytime and night-time voiding frequency, total voided volume, the fraction of urine production during the night (nocturnal polyuria index), and volume of individual voids.

The mean 24-hour urine production is subject to considerable variation. Likewise, circumstantial influence and intra-individual variation cause FVC parameters to fluctuate, though there is comparatively little data [28, 29]. The FVC diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [30-32]. The use of FVCs may cause a ‘bladder training effect’, and influence the frequency of nocturnal voids [33].

The duration of the FVC needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [34]. A systematic review of the available literature recommended FVC should continue for three or more days [35].

Recommendations	LE	GR
Use a bladder diary to assess male LUTS with a prominent storage component or nocturia.	3	B
Tell the patient to complete a bladder diary for the duration of at least three days.	2b	B

4.4 Physical examination and digital-rectal examination

Physical examination to seek potential influences on LUTS, particularly focusing on the suprapubic area, the external genitalia, the perineum and lower limbs should be performed. Urethral discharge, meatal stenosis, phimosis and penile cancer must be excluded.

4.4.1 *Digital-rectal examination and prostate size evaluation*

Digital-rectal examination (DRE) is the simplest way to assess prostate volume, but the correlation to prostate volume is poor. Quality-control procedures for DRE have been described [36]. Transrectal ultrasound (TRUS) is more accurate in determining prostate volume than DRE. Underestimation of prostate volume by DRE increases with increasing TRUS volume, particularly where the volume is > 30 mL [37]. A model of visual aids

has been developed to help urologists estimate prostate volume more accurately [38]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < than 50 mL [39].

Recommendation	LE	GR
Perform a physical examination including digital rectal examination in the assessment of male LUTS.	3	B

4.5 Urinalysis

Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to identify conditions, such as urinary tract infections (UTI), microhaematuria and diabetes mellitus. If abnormal findings are detected further tests are recommended according to other EAU Guidelines, including Guidelines on urinary tract cancers and urological infections [40-43].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [44, 45]. There is limited evidence, yet general expert consensus that the benefits outweigh the costs [46]. The value of urinary dipstick/microscopy for diagnosing UTI in men with LUTS without acute frequency and dysuria has recently been questioned [47].

Recommendation	LE	GR
Use urinalysis (by dipstick or urinary sediment) in the assessment of male LUTS.	3	A*

*Upgraded based on Panel consensus.

4.6 Prostate-specific antigen (PSA)

4.6.1 PSA and the prediction of prostatic volume

Pooled analysis of placebo-controlled BPH trials showed that PSA has a good predictive value for assessing prostate volume, with areas under the curve (AUC) of 0.76-0.78 for various prostate volume thresholds (30 mL, 40 mL, and 50 mL). To achieve a specificity of 70%, whilst maintaining a sensitivity between 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL are PSA > 1.6 ng/mL, > 2.0 ng/mL, and > 2.3 ng/mL, for men with BPH in their 50s, 60s, and 70s, respectively [48].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [49]. A PSA threshold value of 1.5 ng/mL could best predict a prostate volume of > 30 mL, with a positive predictive value (PPV) of 78%. The prediction of prostate volume can also be based on total and free PSA. Both PSA forms predict the TRUS prostate volume (\pm 20%) in > 90% of the cases [50, 51].

4.6.2 PSA and the probability of PCa

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [52]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed.

4.6.3 PSA and the prediction of BPO-related outcomes

Serum PSA is a stronger predictor of prostate growth than prostate volume [53]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow-rate (Q_{max}) [54]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [55].

In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPE-related surgery [56, 57]. An equivalent link was also confirmed by the Olmsted County Study. The risk for treatment was higher in men with a baseline PSA of > 1.4 ng/mL [58]. Patients with BPO seem to have a higher PSA level and larger prostate volumes. The PPV of PSA for the detection of BPO was recently shown to be 68% [59]. Furthermore, in an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [60].

Recommendations	LE	GR
Measure prostate-specific antigen (PSA) if a diagnosis of prostate cancer will change management.	1b	A
Measure PSA if it assists in the treatment and/or decision making process.	1b	A

4.7 Renal function measurement

Renal function may be assessed by serum creatinine or estimated glomerular filtration rate (eGFR). Hydronephrosis, renal insufficiency or urinary retention are more prevalent in patients with signs or symptoms of BPO [61]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [62].

One study reported that 11% of men with LUTS had renal insufficiency [61]. Neither symptom score nor QoL was associated with the serum creatinine level. Diabetes mellitus or hypertension were the most likely causes of the elevated creatinine concentration. Comiter *et al.* [63] reported that non-neurogenic voiding dysfunction is not a risk factor for elevated creatinine levels. Koch *et al.* [64] concluded that only those with an elevated creatinine level require investigational ultrasound (US) of the kidney.

In the Olmsted County community-dwelling men, there was a cross-sectional association between signs and symptoms of BPO (though not prostate volume) and chronic kidney disease (CKD) [65]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max} , a history of hypertension and/or diabetes were associated with CKD [66]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [67]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [68].

Recommendation	LE	GR
Assess renal function if renal impairment is suspected based on history and clinical examination, or in the presence of hydronephrosis, or when considering surgical treatment for male LUTS.	3	A*

*Upgraded based on Panel consensus.

4.8 Post-void residual urine

Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation. Post-void residual is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function (detrusor underactivity) [69, 70]. Using a PVR threshold of 50 mL, the diagnostic accuracy of PVR measurement has a PPV of 63% and a negative predictive value (NPV) of 52% for the predict BOO [71]. A large PVR is not a contraindication to watchful waiting (WW) or medical therapy, although a large PVR may indicate a poor response to treatment and especially to WW. In both the MTOPS and ALTESS studies, a high baseline PVR was associated with an increased risk of symptom progression [56, 57].

Monitoring of changes in PVR over time may allow for identification of patients at risk of acute urinary retention (AUR) [57]. This is of particular importance for the treatment of patients using antimuscarinic medication. In contrast, baseline PVR has little prognostic value for the risk of BPE-related invasive therapy in patients on α 1-blocker or WW [72]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established and this is a research priority.

Recommendation	LE	GR
Measure post-void residual in the assessment of male LUTS.	3	B

4.9 Uroflowmetry

Urinary flow rate assessment is a widely used non-invasive urodynamic test. Key parameters are Q_{max} and flow pattern. Uroflowmetry parameters should preferably be evaluated with voided volume > 150 mL. As Q_{max} is prone to within-subject variation [73, 74], it is useful to repeat uroflowmetry measurements, especially if the voided volume is < 150 mL, or Q_{max} or flow pattern is abnormal.

The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably, and is substantially influenced by threshold values. A threshold Q_{max} of 10 mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15 mL/s was 38%, the PPV 67% and the sensitivity 82% [75]. If Q_{max} is > 15 mL/s, physiological compensatory processes mean that BOO cannot be excluded. Low Q_{max} can arise as a consequence of BOO [76], detrusor underactivity or an under-filled bladder [77]. Therefore, it is limited as a diagnostic test as it is unable to discriminate between the underlying mechanisms. Specificity can be improved by repeated flow rate testing. Uroflowmetry can be used for monitoring treatment outcomes [78] and correlating symptoms with objective findings.

Recommendation	LE	GR
Uroflowmetry in the initial assessment of male LUTS may be performed and should be performed prior to any treatment.	2b	B

4.10 Imaging

4.10.1 Upper urinary tract

Routine imaging of the upper urinary tract in men with LUTS is not recommended, as these men are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population [64, 79-81]. Several arguments support the use of renal US in preference to intravenous urography (IVU). Ultrasound allows for better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, radiation dose and less side effects [79].

Recommendation	LE	GR
Perform ultrasound of the upper urinary tract in men with LUTS and a large post-void residual, or haematuria, or a history of urolithiasis.	3	B

4.10.2 Prostate

Imaging of the prostate can be performed by transabdominal US, TRUS, computed tomography (CT), and magnetic resonance imaging (MRI). However, in daily practice, prostate imaging is performed by transabdominal US or TRUS [79].

4.10.2.1 Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e. open prostatectomy, enucleation techniques, transurethral resection, transurethral incision of the prostate (TUIP), or minimally invasive therapies. It is also important prior to treatment with 5 α -reductase inhibitors (5-ARIs). Prostate volume predicts symptom progression and the risk of complications [81].

Transrectal US is superior to suprapubic (transabdominal) volume measurement [82, 83]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach.

Recommendations	LE	GR
Perform imaging of the prostate (either by transrectal or transabdominal ultrasound) when considering medical treatment for male LUTS, if it assists in the choice of the appropriate drug.	3	B
Perform imaging of the prostate (either by transrectal or transabdominal ultrasound) when considering surgical treatment.	3	B

4.10.3 Voiding cysto-urethrogram

Voiding cysto-urethrogram (VCUG) is not recommended in the routine diagnostic work-up of men with LUTS, but it may be useful for the detection of vesico-ureteral reflux, bladder diverticula, or urethral pathologies. Retrograde urethrography may additionally be useful for the evaluation of urethral strictures where suspected.

4.11 Urethrocystoscopy

Patients with a history of microscopic or gross haematuria, urethral stricture, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation.

Shoukry *et al.* evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [84]. The pre-operative Q_{max} was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had a reduced Q_{max} .

Anikwe showed that there was no significant correlation between the degree of bladder trabeculation (graded from I to IV), and the pre-operative Q_{max} value in 39 symptomatic men aged 53-83 years [85]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [86]. The authors noted a correlation between cystoscopic appearance (grade of bladder trabeculation and urethral occlusion) and urodynamic indices, DO and low compliance. It should be noted, however, that BOO was present in 15% of patients with normal cystoscopic findings, while 8% of patients had no obstruction, even in the presence of severe trabeculation [86].

Recommendation	LE	GR
Perform urethrocytostcopy in men with LUTS to exclude suspected bladder or urethral pathology and/or prior to minimally invasive/surgical therapies if the findings may change treatment.	3	B

4.12 Urodynamics

In male LUTS, the most widespread invasive urodynamic techniques employed are filling cystometry and pressure flow studies (PFS). The major goal of urodynamics is to explore the functional mechanisms of LUTS and to identify risk factors for adverse outcomes (for informed/shared decision-making). Most terms and conditions (e.g. DO, low compliance, BOO/BPO, DUA) are defined by urodynamic investigation.

4.12.1 Diagnosing bladder outlet obstruction

Pressure flow studies are the basis for the definition of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. Bladder outlet obstruction/BPO has to be differentiated from DUA, which signifies decreased detrusor pressure during voiding in combination with decreased urinary flow rate [2].

Urodynamic testing may also identify DO. Studies have described an association between BOO and DO [87, 88]. In men with LUTS attributed to BPE, DO was present in 61% and independently associated with BOO grade and ageing [87].

The prevalence of DUA in men with LUTS is 11-40% [89, 90]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [91, 92]. There are no published RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with PFS with respect to the outcome of treatment but one such study is ongoing in the UK.

A Cochrane meta-analysis was done to determine whether performing invasive urodynamic investigation reduces the number of men with continuing symptoms of voiding dysfunction. Two trials with 350 patients were included. Invasive urodynamic testing changed clinical decision making, patients who underwent urodynamics were less likely to undergo surgery; however, no evidence was found to demonstrate whether this led to reduced symptoms of voiding dysfunction after treatment [93].

Due to the invasive nature of the test, a urodynamic investigation is generally only offered if conservative treatment has failed. The Guidelines Panel attempted to identify specific indications for PFS based on age, findings from other diagnostic tests, and previous treatments. The Panel allocated a different degree of obligation for PFS in men > 80 years and men < 50 years, which may reflect the lack of evidence. In addition, there was no consensus whether PFS should or may be performed when considering surgery in men with bothersome predominantly voiding LUTS and $Q_{max} > 10$ mL/s, although the Panel recognised that with a $Q_{max} < 10$ mL/s, BOO is likely and PFS is not necessarily needed.

Patients with neurological disease, including those with previous radical pelvic surgery, should be assessed according to the EAU Guidelines on Neuro-Urology [94].

4.12.2 Videourodynamics

Videourodynamics provides additional anatomical and functional information and may be recommended if the clinician considers this is needed to understand the pathophysiological mechanism of an individual patient's LUTS.

Recommendations	LE	GR
Perform pressure-flow studies (PFS) only in individual patients with specific indications prior to invasive treatment or when evaluation of the underlying pathophysiology of LUTS is warranted.	3	B
Perform PFS in men who have had previously unsuccessful (invasive) treatment for LUTS.	3	B
When considering invasive treatment, pressure-flow studies may be used for patients who cannot void > 150 mL.	3	C
When considering invasive treatment in men with bothersome voiding LUTS, PFS may be performed in men with a post-void residual > 300 mL.	3	C
When considering invasive treatment in men with bothersome, predominantly voiding LUTS, PFS may be performed in men aged > 80 years.	3	C
When considering invasive treatment in men with bothersome, predominantly voiding LUTS, perform PFS in men aged < 50 years.	3	B

4.13 Non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS

4.13.1 *Prostatic configuration/intravesical prostatic protrusion (IPP)*

Prostatic configuration can be evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [95]. The PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward one as the prostate becomes more circular. The sensitivity of PCAR was 77% for diagnosing BPO when PCAR was > 0.8 , with 75% specificity [95].

Ultrasound measurement of IPP assesses the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a suprapubically positioned US scanner, with a bladder volume of 150-250 mL; grade I protrusion is 0-4.9 mm, grade II is 5-10 mm and grade III is > 10 mm.

Intravesical prostatic protrusion correlates well with BPO (presence and severity) on urodynamic testing, with a PPV of 94% and a NPV of 79% [96]. Intravesical prostatic protrusion may also correlate with prostate volume, DO, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [97]. Furthermore, IPP also appears to successfully predict the outcome of a trial without catheter (TWOC) after AUR [98, 99]. However, no information with regard to intra- or inter-observer variability and learning curve is yet available. Therefore, IPP may be a feasible option to infer BPO in men with LUTS. The role of IPP as a non-invasive alternative to PFS in the assessment of male LUTS is under evaluation.

4.13.2 *Bladder/detrusor wall thickness and ultrasound-estimated bladder weight*

For bladder wall thickness (BWT) assessment, the distance between the mucosa and the adventitia is measured. For detrusor wall thickness (DWT) assessment, the only measurement needed is the detrusor sandwiched between the mucosa and adventitia [100].

A correlation between BWT and PFS parameters has been reported. A threshold value of 5 mm at the anterior bladder wall with a bladder filling of 150 mL was best at differentiating between patients with or without BOO [101]. Detrusor wall thickness at the anterior bladder wall with a bladder filling > 250 mL (threshold value for BOO > 2 mm) has a PPV of 94% and a specificity of 95%, achieving 89% agreement with PFS [71]. Threshold values of 2.0, 2.5, or 2.9 mm for DWT in patients with LUTS are able to identify 81%, 89%, and 100% of patients with BOO, respectively [102].

All studies found that BWT or DWT measurements have a higher diagnostic accuracy for detecting BOO than Q_{max} or Q_{ave} of free uroflowmetry, measurements of PVR, prostate volume, or symptom severity. One study could not demonstrate any difference in BWT between patients with normal urodynamics, BOO or DO. However, the study did not use a specific bladder filling volume for measuring BWT [103]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [104]. Measurement of BWT/DWT is therefore not recommended for the diagnostic work-up of men with LUTS.

Ultrasound-estimated bladder weight (UEBW) may identify BOO with a diagnostic accuracy of 86% at a cut-off value of 35 g [105, 106]. Severe LUTS and a high UEBW (> 35 g) are risk factors for prostate/BPH surgery in men on α -blockers [107].

4.13.3 *Non-invasive pressure-flow testing*

The penile cuff method, in which flow is interrupted to estimate isovolumetric bladder pressure, shows promising data, with good test repeatability [108] and interobserver agreement [109]. A nomogram has also been derived [110] whilst a method in which flow is not interrupted is also under investigation [111].

The data generated with the external condom method [112] correlates with invasive PFS in a high proportion of patients [113]. Resistive index [114] and prostatic urethral angle [115] have also been proposed, but are still experimental.

4.13.4 *The diagnostic performance of non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS compared with pressure-flow studies*

The diagnostic performance of non-invasive tests in diagnosing BOO in men with LUTS compared with PFS has been investigated by a systematic review performed by the Panel [116].

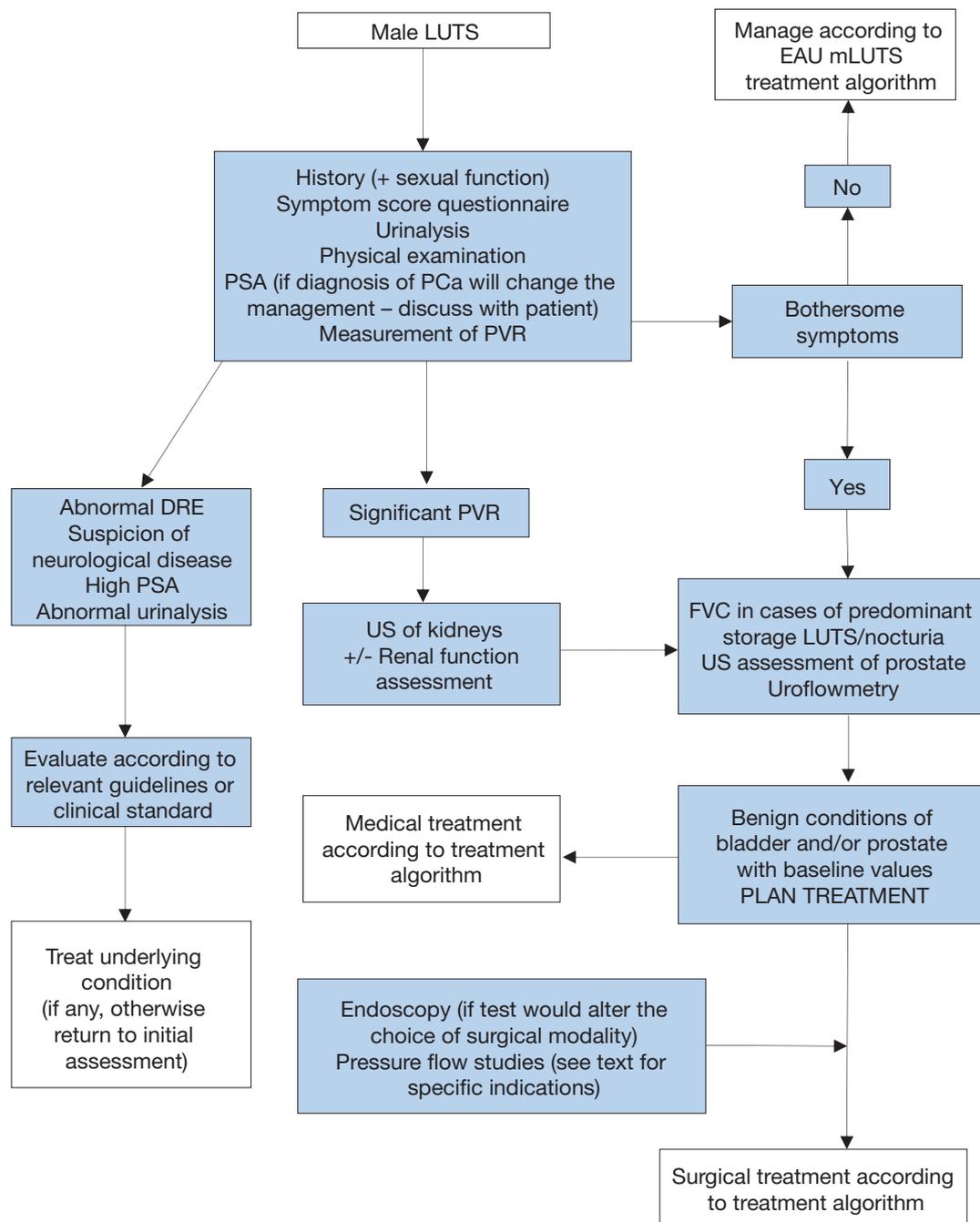
A total of 42 studies were included in this review, this summary print version is supplemented by a detailed online version (<http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/>). The majority were prospective cohort studies, and the diagnostic accuracy of the following non-invasive tests were assessed: penile cuff test; uroflowmetry; detrusor/bladder wall thickness; bladder weight; external condom catheter method; IPP; doppler US; prostate volume/height; near-infrared spectroscopy. Overall, although the majority of studies have a low risk of bias, data regarding the diagnostic accuracy of these non-invasive tests is limited by the heterogeneity of the studies in terms of the threshold values used to define BOO, the different urodynamic definitions of BOO used across different studies and the small number of studies for each test. It was found that specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable. Therefore, even though

several tests have shown promising results regarding non-invasive diagnosis of BOO, invasive urodynamics remains the modality of choice.

Recommendation	LE	GR
None of the non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS can currently be recommended as an alternative to pressure-flow studies.	1a	B

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older

Readers are strongly recommended to read the full text that highlights the current position of each test in detail.



DRE = digital-rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms; PCa = prostate cancer; PSA = prostate specific antigen; PVR = post-void residual; US = ultrasound.

5. DISEASE MANAGEMENT

5.1 Conservative treatment

5.1.1 Watchful waiting

Many men with LUTS are not troubled enough by their symptoms to need drug treatment or surgical intervention. All men with LUTS should be formally assessed prior to any allocation of treatment in order to establish symptom severity and to differentiate between men with uncomplicated (the majority) and complicated LUTS. Watchful waiting is a viable option for many men with non-bothersome LUTS as few will progress to AUR and complications (e.g. renal insufficiency or stones) [117, 118], whilst others can remain stable for years [119]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [120].

A study comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed the surgical group had improved bladder function (flow rates and PVR volumes), especially in those with high levels of bother; 36% of WW patients crossed over to surgery within five years, leaving 64% doing well in the WW group [121, 122]. Increasing symptom bother and PVR volumes are the strongest predictors of clinical failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW.

5.1.2 Behavioural and dietary modifications

It is customary for this type of management to include the following components:

- education (about the patient's condition);
- reassurance (that cancer is not a cause of the urinary symptoms);
- periodic monitoring;
- lifestyle advice [119, 120, 123, 124] such as:
 - o reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g. at night or when going out in public);
 - o avoidance/moderation of intake of caffeine or alcohol, which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia;
 - o use of relaxed and double-voiding techniques;
 - o urethral milking to prevent post-micturition dribble;
 - o distraction techniques such as penile squeeze, breathing exercises, perineal pressure, and mental tricks to take the mind off the bladder and toilet, to help control storage symptoms;
 - o bladder retraining that encourages men to hold on when they have sensory urgency to increase their bladder capacity and the time between voids;
 - o reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects (these recommendations apply especially to diuretics);
 - o providing necessary assistance when there is impairment of dexterity, mobility, or mental state;
 - o treatment of constipation.

There now exists evidence (LE: 1b) that self-management as part of WW reduces both symptoms and progression [123, 124] (online supplementary Table S.12). Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care only for up to a year [123].

5.1.3 Practical considerations

The components of self-management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [125]. Further research in this area is required.

Recommendations	LE	GR
Offer men with mild/moderate symptoms, minimally bothered by their symptoms, watchful waiting.	1b	A
Offer men with LUTS lifestyle advice prior to or concurrent with treatment.	1b	A

5.2 Pharmacological treatment

5.2.1 α 1-Adrenoceptor antagonists (α 1-blockers)

Mechanism of action: α 1-blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO [126]. However, α 1-blockers have little effect on urodynamically determined bladder outlet resistance [127], and treatment-associated improvement of LUTS correlates poorly with obstruction [128]. Thus, other mechanisms of action may be relevant.

α 1-adrenoceptors located outside the prostate (e.g. urinary bladder and/or spinal cord) and α 1-adrenoceptor subtypes (α 1B- or α 1D-adrenoceptors) may play a role as mediators of effects. α 1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events.

α 1-blockers currently available are: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin). α 1-blockers exist in different formulations (online supplementary Table S.13). Although different formulations result in different pharmacokinetic and tolerability profiles, the overall clinical impact of the different formulations is modest.

Efficacy: Indirect comparisons and limited direct comparisons between α 1-blockers demonstrate that all α 1-blockers have a similar efficacy in appropriate doses [129]. Effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [130].

Controlled studies show that α 1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25% (online supplementary Table S.14). However, considerable improvements also occurred in the corresponding placebo arms [55, 130]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [55, 130].

α 1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α 1-blocker efficacy in studies with follow-up periods of less than one year, but α 1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [56, 131-134]. α 1-blocker efficacy is similar across age groups [130]. α 1-blockers neither reduce prostate size nor prevent AUR in long-term studies [132-134]. Nevertheless, IPSS reduction and Q_{max} improvement during α 1-blocker treatment appears to be maintained over at least four years.

Tolerability and safety: Tissue distribution, subtype selectivity, and pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α 1-blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin, and are less common for alfuzosin and tamsulosin [135]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α 1-blocker-induced vasodilatation [136]. In contrast, the frequency of hypotension with the α 1A- selective blocker silodosin is comparable with placebo [137]. In a large retrospective cohort analysis of men aged \geq 66 years treated with α 1-blockers, the risks of falling (odds ratio [OR] 1.14) and of sustaining a fracture (OR 1.16) was increased, most likely as a result of induced hypotension [138].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [139]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α 1-blockers [140]. However, the OR for IFIS was much higher for tamsulosin. It appears prudent not to initiate α 1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α 1-blocker use.

A systematic review concluded that α 1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation [141]. Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor. In a recent meta-analysis ejaculatory dysfunction (EjD) was significantly more common with α 1-blockers than with placebo (OR 5.88). In particular, EjD was significantly more commonly related with tamsulosin or silodosin (OR: 8.57 and 32.5) than placebo, while both doxazosin and terazosin (OR 0.80 and 1.78) were associated with a low risk of EjD [142]. In the meta-regression, the occurrence of EjD was independently associated with the improvement of urinary symptoms and flow rate, suggesting that the more effective the α 1-blocker is the greater the incidence of EjD.

Practical considerations: α 1-blockers are often considered the first line drug treatment of male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events. However, α 1-blockers do not prevent occurrence of urinary retention or need for surgery. Ophthalmologists should be informed about α 1-blocker use prior to cataract surgery. Elderly patients treated with non-selective α 1-blockers should be informed about the risk of orthostatic hypotension. Sexually active patients treated with selective α 1-blockers should be counselled about the risk of EjD.

Recommendations	LE	GR
Offer α 1-blockers to men with moderate-to-severe LUTS.	1a	A
Counsel patients about the treatment related side effects associated with selective versus non-selective α -blockers.	1a	A

5.2.2 5α -reductase inhibitors

Mechanism of action: Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted from testosterone by the enzyme 5α -reductase, a nuclear-bound steroid enzyme [143]. Two isoforms of this enzyme exist:

- 5α -reductase type 1, with minor expression and activity in the prostate but predominant activity in extraprostatic tissues, such as skin and liver.
- 5α -reductase type 2, with predominant expression and activity in the prostate.

Two 5α -reductase inhibitors (5-ARIs) are available for clinical use: dutasteride and finasteride (online supplementary Table S.15). Finasteride inhibits only 5α -reductase type 2, whereas dutasteride inhibits 5α -reductase types 1 and 2 with similar potency (dual 5-ARI). 5-ARIs act by inducing apoptosis of prostate epithelial cells [144] leading to prostate size reduction of about 18-28% and a decrease in circulating PSA levels of about 50% after six to twelve months of treatment [145]. Mean prostate volume reduction and PSA decrease may be even more pronounced after long-term treatment. Continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5-ARIs.

Efficacy: Clinical effects relative to placebo are seen after a minimum treatment duration of at least six to twelve months. After two to four years of treatment, 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by 18-28%, and increase Q_{max} by 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement (online supplementary Table S.16) [56, 133, 134, 146-152]. A indirect comparison and one direct comparative trial (twelve months duration) indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [145, 153]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [154]. However, dutasteride seems to reduce IPSS, prostate volume, and the risk of AUR, and to increase Q_{max} even in patients with prostate volumes of between 30 and 40 mL at baseline [155, 156]. A long-term trial with dutasteride in symptomatic men with prostate volumes > 30 mL and increased risk for disease progression showed that dutasteride reduced LUTS at least as much as, or even more effectively than, the α 1-blocker tamsulosin [133, 152, 157]. The greater the baseline prostate volume (or serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride as compared to tamsulosin.

5-ARIs, but not α 1-blockers, reduce the long-term (> one year) risk of AUR or need for surgery [56, 150, 158]. In the PLESS study, finasteride treatment reduced the relative risk of AUR by 57%, and surgery by 55% at four years, compared with placebo [150]. In the MTOPS study, a significant reduction in the risk of AUR and surgery in the finasteride arm compared with placebo was reported (68% and 64%, respectively) [56]. A pooled analysis of randomised trials with two-year follow-up data, reported that treatment with finasteride significantly decreased the occurrence of AUR by 57%, and surgical intervention by 34%, in moderately symptomatic LUTS [159]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [160, 161].

Finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation [162].

Tolerability and safety: The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, erectile dysfunction (ED) and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [56, 134, 145]. The incidence of sexual dysfunction and other adverse events is low and even decreased with trial duration. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients.

Data from two trials on PCa chemoprevention (the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trial) found a higher incidence of high-grade cancers in the 5-ARIs arms [163, 164]. Although no causal relationship with high-grade PCa has been proven, men taking 5-ARIs should be followed-up regularly using serial PSA testing and any confirmed PSA increase should be evaluated accordingly. There is a long-standing debate regarding potential cardiovascular side effects of 5-ARIs, in particular dutasteride [165]. In a five year population-based study performed in Taiwan, Hsieh *et al.* could not identify an association between the use of 5-ARIs and increased cardiovascular side effects, in elderly men (> 65 years) [165].

Practical considerations: Treatment with 5-ARIs should be considered in men with moderate-to-severe LUTS

and an enlarged prostate (> 40 mL) and/or elevated PSA concentration (> 1.4-1.6 ng/mL). 5 α -reductase inhibitors can prevent disease progression with regard to acute urinary retention and the need for surgery. Due to the slow onset of action, they are suitable only for long-term treatment (years). Their effect on the serum PSA concentration needs to be considered in relation to PCa screening.

Recommendations	LE	GR
Use 5 α -reductase inhibitors in men who have moderate-to-severe LUTS and an enlarged prostate (> 40 mL).	1b	A
Counsel patients about the delayed symptom improvement with 5 α -reductase inhibitors.	1a	A

5.2.3 Muscarinic receptor antagonists

Mechanism of action: The detrusor is innervated by parasympathetic nerves whose main neurotransmitter is acetylcholine, which stimulates muscarinic receptors (M-cholinoreceptors) on the smooth muscle cells. Muscarinic receptors are also present on other cell types, such as bladder urothelial cells, epithelial cells of the salivary glands, or the peripheral or central nervous system. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. M2 are more numerous, but the M3 subtype is functionally more important in bladder contractions in healthy humans [166, 167]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [168, 169].

The following muscarinic receptor antagonists are licensed for treating overactive bladder/storage symptoms (online supplementary Table S.17): darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); trospium chloride. Transdermal preparations of oxybutynin have been formulated and evaluated in clinical trials [170, 171].

Efficacy: Antimuscarinics were mainly tested in females in the past, as it was believed that LUTS in men were caused by the prostate, so should be treated with prostate-specific drugs. However, there is no scientific data for this assumption [172]. A sub-analysis of an open-label trial of OAB patients showed that age but not gender had an impact on urgency, frequency, or urgency incontinence [173]. In a pooled analysis, which included a sub-analysis of male patients, fesoterodine 8 mg was superior to tolterodine extended release (ER) 4 mg for the improvement of severe urgency episodes/24 hours and the OAB-q Symptom Bother score at week twelve, the urinary retention rate was around 2% [174].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO have been tested (online supplementary Table S.18) [175-180]. Most trials lasted only twelve weeks. Four post hoc analyses of large RCTs on the treatment of OAB in women and men without presumed BOO were performed focusing only on the men [176, 178, 181]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency and urgency-related voiding whilst improving patient perception of treatment benefit. Solifenacin significantly improved mean patient perception of bladder condition scores, mean OAB questionnaire scores, and overall perception of bladder problems. Fesoterodine improved micturition frequency, urgency episodes, and urgency urinary incontinence (UUI) episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after 12-25 weeks [177, 180].

In the Tolterodine and Tamsulosin in Men with LUTS including OAB: Evaluation of Efficacy and Safety Study, men who received tolterodine monotherapy saw improvement only in urgency incontinence, but not urgency, IPSS (total or storage subscore), or the overall percentage of patients reporting treatment benefit compared with placebo [179].

A further analysis showed that men with PSA levels of < 1.3 ng/mL (smaller prostates) might benefit more from antimuscarinic drugs [182]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [180, 183]. In a small RCT without placebo, propiverine improved frequency and urgency episodes [183]. In an open-label study, tolterodine decreased 24-hour micturition, nocturia and American Urological Association Symptom Index scores [180].

Tolerability and safety: Antimuscarinic drug trials generally show approximately 3-10% withdrawals, which is similar to placebo. Drug-related adverse events include dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%), nasopharyngitis (up to 3%), and dizziness (up to 5%).

Increased PVR in men without BOO is minimal and similar to placebo. Nevertheless, fesoterodine 8 mg showed higher PVRs (+20.2 mL) than placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) [179]. Incidence of urinary retention in men without BOO was similar to placebo for tolterodine (0-1.3% vs. 0-1.4%). With fesoterodine 8 mg, 5.3% had symptoms, which was higher than placebo or fesoterodine 4 mg (both 0.8%).

These symptoms appeared during the first two weeks of treatment and mainly affected men aged 66 years or older.

Theoretically antimuscarinics might decrease bladder strength, and hence might be associated with PVR urine or urinary retention. A twelve week safety study on men with mild to moderate BOO showed that tolterodine increased the PVR (49 mL vs. 16 mL) but not acute urinary retention (3% in both arms) [184]. The urodynamic effects included larger bladder volumes at first detrusor contraction, higher maximum cystometric capacity, and decreased bladder contractility index. Q_{max} was unchanged. This trial indicated that short-term treatment with antimuscarinics in men with BOO is safe [184].

Practical considerations: Not all antimuscarinics have been tested in elderly men, and long-term studies on the efficacy of muscarinic receptor antagonists in men of any age with LUTS are not yet available. In addition, only patients with low PVR volumes at baseline were included in the studies. These drugs should therefore be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised. Men should be advised to discontinue medication if worsening voiding LUTS or urinary stream is noted after initiation of therapy.

Recommendations	LE	GR
Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	1b	B
Prescribe antimuscarinics with caution in men with a post-void residual volume > 150 mL.	4	C

5.2.4 Phosphodiesterase 5 inhibitors

Mechanism of action: Phosphodiesterase 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDEs might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [185]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the LUT [186]. Finally, PDE5Is could reduce chronic inflammation in the prostate and bladder [187]. The exact mechanism of PDE5Is on LUTS remains unclear.

Available drugs: Although clinical trials of several selective oral PDE5Is have been conducted in men with LUTS, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS.

Efficacy: Several RCTs have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and improve QoL (online supplementary Table S.19). However, Q_{max} did not significantly differ from placebo in most trials. In a meta-analysis, PDE5Is were found to improve IPSS and IIEF score, but not Q_{max} [188].

Tadalafil 5 mg reduces IPSS by 22-37% (online supplementary Table S.19), and improvement may be seen within a week of initiation of treatment [189]. A three point or greater total IPSS improvement was observed in 59.8% of tadalafil treated men within one week and in 79.3% within four weeks [190]. The maximum trial (open label) duration was 52 weeks [191]. A subgroup analysis of pooled data from four RCTs demonstrated a significant reduction in LUTS, regardless of baseline severity, age, previous use of α -blockers or PDE5Is, total testosterone level or predicted prostate volume [192]. In a recent post hoc analysis of pooled data from four RCTs, tadalafil was shown to also be effective in men with cardiovascular risk factors/comorbidities except for patients receiving more than one antihypertensive medication. The use of diuretics may contribute to patients' perception of a negated efficacy [193]. Among sexually active men > 45 years with comorbid LUTS/BPH and ED, tadalafil improved both conditions [194].

An integrated data analyses from four placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%, $p < 0.001$) vs. indirect (7.5%, $p = 0.32$) treatment effects via IIEF-EF improvement [195]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [196].

A combination of PDE5Is and α -blockers has also been evaluated. A meta-analysis of five RCTs (two studies with tadalafil 20 mg, two with sildenafil 25 mg, and one with vardenafil 20 mg), showed that combination therapy significantly improved IPSS score (-1.8), IIEF score (+3.6) and Q_{max} (+1.5 mL/s) compared with α -blockers alone [188]. The effects of tadalafil 5 mg combined with finasteride 5 mg were assessed in a 26-week placebo-controlled RCT. The combination of tadalafil and finasteride provided an early improvement in urinary symptoms ($p < 0.022$ after 4, 12 and 26 weeks), with a significant improvement of storage and voiding symptoms and QoL. Combination therapy was well tolerated and improved erectile function [197]. However, only tadalafil 5 mg has been licensed in the context of LUTS management while data on combinations of PDE5Is and other LUTS medications is emerging.

Tolerability and safety: Reported adverse effects in RCTs comparing the effect of all PDE5Is vs. placebo in men with LUTS include flushing, gastroesophageal reflux, headache, dyspepsia, back pain and nasal congestion [188]. Discontinuation rate due to adverse effects for tadalafil was 2.0% [198] and did not differ by age, LUTS severity, testosterone levels, or prostate volume in the pooled data analyses [192].

PDE5Is are contraindicated in patients using nitrates, the potassium channel opener nicorandil, or the α 1-blockers doxazosin and terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (< three months) or stroke (< six months), myocardial insufficiency (New York Heart Association stage > 2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is.

Practical considerations: To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without ED. The meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is [188]. Long-term experience with tadalafil in men with LUTS is limited to one trial with a one year follow-up [191], therefore conclusions about its efficacy or tolerability greater than one year are not possible. There is limited information on reduction of prostate size and no data on disease progression.

Recommendation	LE	GR
Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction.	1a	A

5.2.5 **Plant extracts - phytotherapy**

Mechanism of action: Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits. There are single plant preparations (mono-preparations) and preparations combining two or more plants in one pill (combination preparations). The most widely used plants are Cucurbita pepo (pumpkin seeds), Hypoxis rooperi (South African star grass), Pygeum africanum (bark of the African plum tree), Secale cereale (rye pollen), Serenoa repens (syn. Sabal serrulata; saw palmetto) and Urtica dioica (roots of the stinging nettle).

Possible relevant compounds include phytosterols, β -sitosterol, fatty acids, and lectins [199]. *In vitro*, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects; decrease sexual hormone binding globulin; inhibit aromatase, lipoxigenase, growth factor-stimulated proliferation of prostatic cells, α -adrenoceptors, 5 α -reductase, muscarinic cholinceptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [199-201]. These effects have not been confirmed *in vivo*, and the precise mechanisms of plant extracts remain unclear.

Efficacy: The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects, therefore the effects of one brand cannot be extrapolated to others [202]. In addition, batches from the same producer may contain different concentrations of active ingredients [203]. A review of recent extraction techniques and their impact on the composition/biological activity of Serenoa repens based available products showed that results from different clinical trials must be compared strictly according to the same validated extraction technique and/or content of active compounds [204]. Thus the pharmacokinetic properties can vary significantly.

Online supplementary Table S.20 presents the trials with the highest LE for each plant extract. In general, no phytotherapeutic agent has been shown to reduce prostate size, and no trial has proven a reduction of BOO or a decrease in disease progression.

A cochrane meta-analyses suggest that men treated with Pygeum africanum were twice as likely to report symptom improvement whilst men treated with Secale cereale were twice as likely to benefit from therapy compared to placebo and that Serenoa repens was not superior to placebo, finasteride, or tamsulosin for IPSS (similar levels of IPSS improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence) [205-207].

Recently, short-term studies on the combination of plant extracts with tamsulosin have been published with promising results [208, 209]. Combination treatment with Serenoa Repens (SeR), lycopene (Ly), selenium (Se) and tamsulosin was more effective than single therapies (SeR-Ly-Se or tamsulosin) in improving IPSS and increasing Q_{max} in patients with LUTS at twelve months. The combination treatment of Serenoa repens and tamsulosin was shown to be more effective than tamsulosin monotherapy in reducing storage symptoms but changes in IPSS, voiding subscore, QoL, Q_{max} , PVR, PSA, and prostate volume showed no significant differences between the two groups.

Tolerability and safety: Side-effects during phytotherapy are generally mild and comparable to placebo. Serious adverse events were not related to the study medication. Gastrointestinal complaints were the most commonly reported. In formulations with *Hypoxis rooperi*, ED was reported in 0.5% of patients.

Practical considerations: Phytotherapeutic agents are a heterogeneous group and may contain differing concentrations of active ingredients. Hence, meta-analyses may not be justified and results of any analyses have to be interpreted with caution.

Panel interpretation: The Guidelines Panel has not made any specific recommendations on phytotherapy for the treatment of male LUTS due to product heterogeneity, a limited regulatory framework, and methodological limitations of the published trials and meta-analyses.

5.2.6 **Beta-3 agonist**

Mechanism of action: Beta-3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation.

Efficacy: Mirabegron 50 mg is the first clinically available beta-3 agonist with approval for use in adults with OAB. Mirabegron has undergone extensive evaluation in RCTs conducted in Europe, Australia, North America and Japan [210-214]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency incontinence, and urgency and also patient perception of treatment benefit. These studies had a predominantly female study population.

Mirabegron as an add-on therapy has been studied in OAB patients with incontinence despite antimuscarinic therapy [215], again in a predominantly-female study population. An Asian study with a higher proportion of male subjects (approximately one third) reported superiority over placebo in reducing frequency of micturition, but did not report the results separately for the genders [216].

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [210-213]. Mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure \geq 180 mmHg or diastolic blood pressure \geq 110 mmHg, or both). Blood pressure should be measured before starting treatment and monitored regularly during treatment. The proportion of patients with dry mouth and constipation in the mirabegron groups was notably lower than reported in RCTs of other OAB agents or of the active control tolterodine [210]. Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron did not adversely affect voiding urodynamic parameters compared to placebo in terms of Q_{max} , detrusor pressure at maximum flow and bladder contractility index [217]. The overall change in PVR with mirabegron is small [217].

Practical considerations: Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. Studies on the use of mirabegron in combination with other pharmacotherapeutic agents for male LUTS are pending. However, pharmacokinetic interaction upon add-on of mirabegron or tamsulosin to existing tamsulosin or mirabegron therapy does not cause clinically relevant changes in safety profiles [218]. One small study has looked at change in symptom scores in men receiving mirabegron with tamsulosin 0.2 mg daily [219]. A phase four study, with a small proportion of male subjects, reported addition of mirabegron in people with persisting urgency despite solifenacin in a Japanese population [220].

Recommendation	LE	GR
Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	1b	B

5.2.7 **Combination therapies**

5.2.7.1 *α 1-blockers + 5 α -reductase inhibitors*

Mechanism of action: Combination therapy consists of an α 1-blocker (Section 5.2.1) together with a 5-ARI (Section 5.2.2). The α 1-blocker exhibits clinical effects within hours or days, whereas the 5-ARI needs several months to develop full clinical efficacy. Finasteride has been tested in clinical trials with alfuzosin, terazosin, doxazosin or terazosin, and dutasteride with tamsulosin.

Efficacy: Several studies have investigated the efficacy of combination therapy against an α 1-blocker, 5-ARI or placebo alone (online supplementary Table S.21). Initial studies with follow-up periods of six to twelve months demonstrated that the α 1-blocker was superior to finasteride in symptom reduction, whereas combination therapy of both agents was not superior to α 1-blocker monotherapy [147, 148, 221]. In studies with a placebo

arm, the α 1-blocker was consistently more effective than placebo, but finasteride was not. Data at one year in the MTOPS study showed similar results [56].

Long-term data (four years) from MTOPS, and Combination of Avodart and Tamsulosin (CombAT) studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max} , and superior to α -blocker alone in reducing the risk of AUR or need for surgery [56, 133, 134].

The CombAT study demonstrated that combination treatment is superior to either monotherapy regarding symptoms and flow rate starting from month nine, and superior to α 1-blocker for AUR and the need for surgery after eight months [134]. Thus the differences in MTOPS may reflect different inclusion and exclusion criteria and baseline patient characteristics.

Discontinuation of the α 1-blocker after six to nine months of combination therapy was investigated by an RCT and an open-label multicentre trial [222, 223]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [222], with almost three-quarters of patients reporting no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy.

A more recent trial evaluated the symptomatic outcome of finasteride monotherapy at three and nine months after discontinuation of nine-month combination therapy [223]. LUTS improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.4). The limitations of the studies include the short duration and the short follow-up period after discontinuation.

In both the MTOPS and CombAT studies, combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, AUR, UTI, incontinence, or an increase in creatinine > 50%. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy vs. placebo and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [56]. In addition, finasteride (alone or in combination), but not doxazosin, significantly reduced both the risks of AUR and the need for BPH related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years [224]. To prevent one case of urinary retention and/or surgical treatment thirteen patients need to be treated for four years with dutasteride and tamsulosin combination therapy compared to tamsulosin monotherapy while the absolute risk reduction (risk difference) was 7.7%.

The CONDUCT study compared efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin to a WW approach with the potential initiation of tamsulosin (step-up approach) in a two year RCT with a total of 742 patients. In both arms detailed lifestyle advice was given. This fixed-dose combination resulted in a rapid and sustained improvement in men with moderate LUTS at risk of disease progression, the difference in IPSS at 24 months was 1.8 points ($p < 0.001$) [225]. Furthermore, tamsulosin plus dutasteride significantly reduced the relative risk of clinical progression (mainly characterised as a worsening in symptoms) by 43.1% when compared with WW, with an absolute risk reduction of 11.3% (number needed to treat [NNT] = 9).

The influence of baseline variables on changes in IPSS after combination therapy with dutasteride plus tamsulosin or either monotherapy was tested based on the four year results of the CombAT study. Combination therapy provided consistent improvement of LUTS over tamsulosin across all analysed baseline variables at 48 months [226].

More recently, a combination of the 5-ARI, finasteride, and tadalafil 5 mg was tested in a large scale RCT against finasteride monotherapy. This study supports the concept of this novel combination therapy and is described in more detail in the chapter on PDE5Is [197].

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [56, 133, 134]. The adverse events observed during combination treatment were typical of α 1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy.

Practical considerations: Compared with α 1-blockers or 5-ARI monotherapy, combination therapy results in a greater improvement in LUTS and increase in Q_{max} , and is superior in prevention of disease progression. However, combination therapy is also associated with a higher rate of adverse events. Combination therapy should therefore be prescribed primarily in men who have moderate-to-severe LUTS and are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, higher PVR, lower Q_{max} , etc.). Combination therapy should only be used when long-term treatment (more than twelve months) is intended and patients should be informed about this. Discontinuation of the α 1-blocker after six months might be considered in men with moderate LUTS.

Recommendation	LE	GR
Use combination treatment of an α 1-blocker and 5 α -reductase inhibitor in men with moderate-to-severe LUTS and risk of disease progression (e.g. prostate volume > 40 mL).	1b	A

5.2.7.2 α 1-blockers + muscarinic receptor antagonists

Mechanism of action: Combination treatment consists of an α 1-blocker together with an antimuscarinic aiming to antagonise both α 1-adrenoceptors and muscarinic receptors. The possible combinations have not all been tested in clinical trials yet.

Efficacy: Several RCTs and prospective studies investigated combination therapy, lasting four to twelve weeks, either as an initial treatment in men with OAB and presumed BPO or as a sequential treatment for storage symptoms persisting while on an α 1-blocker [179, 180, 224, 227-233] (online supplementary Table S.22). One trial used the α 1-blocker naftopidil (not registered in most European countries) with and without antimuscarinics [234]. A high proportion of men with voiding and storage LUTS need to add anticholinergics after α 1-blocker monotherapy, particularly those with longer duration of symptoms at presentation, and men with storage symptoms and a small prostate volume [235].

Combination treatment is more efficacious in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α 1-blockers or placebo alone, and improves QoL [179, 236]. Symptom improvement is higher regardless of PSA concentration, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3 ng/mL [182].

Persistent LUTS during α 1-blocker treatment can be reduced by the additional use of an antimuscarinic, [180, 224, 227, 233, 237, 238]. Two systematic reviews of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [239, 240]. Effectiveness of therapy is evident primarily in those men with moderate-to-severe storage LUTS [241]. Long term use of combination therapy has been reported in patients receiving treatment for up to a year, showing symptomatic response is maintained, with a low incidence of AUR [242]. In men with moderate-to-severe storage symptoms, voiding symptoms and PVR < 150 mL, the reduction in symptoms using combination therapy is associated with patient-relevant improvements in health related quality of life (HRQoL) compared with placebo and α 1-blocker monotherapy [243].

Tolerability and safety: Adverse events of both drug classes are seen with combined treatment using α 1-blockers and antimuscarinics. The most common side-effect is xerostomia. Some side-effects (e.g. xerostomia or ejaculation failure) may show increased incidence which cannot simply be explained by summing the incidence with the drugs used separately. Increased PVR may be seen, but is usually not clinically significant, and risk of AUR is low [239, 240]. Antimuscarinics do not cause evident deterioration in maximum flow rate used in conjunction with an α 1-blocker in men with OAB symptoms [236, 244].

A recent RCT investigated safety in terms of maximum detrusor pressure and Q_{max} for solifenacin (6 mg or 9 mg) with tamsulosin in men with LUTS and BOO compared with placebo [245]. The combination therapy was not inferior to placebo for the primary urodynamic variables; Q_{max} was increased versus placebo [245].

Practical considerations: Class effects are likely to underlie efficacy and QoL using an α 1-blocker and antimuscarinic. Trials used mainly storage symptom endpoints, were of short duration, and included only men with low PVR volumes at baseline. Therefore, measuring PVR is recommended during combination treatment.

Recommendations	LE	GR
Use combination treatment of an α 1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.	1b	B
Prescribe combination treatment with caution in men with a post-void residual volume > 150 mL.	2b	B

5.3 Surgical treatment

5.3.1 **Transurethral resection of the prostate and transurethral incision of the prostate**

Mechanism of action: Transurethral resection of the prostate removes tissue from the transition zone of the gland. Transurethral incision of the prostate (TUIP) involves incising the bladder outlet without tissue removal. This technique may replace TURP in selected cases, especially in prostate sizes < 30 mL without a middle lobe.

Efficacy: In a recent analysis of 20 contemporary RCTs with a maximum follow-up of five years, TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [246]. TURP delivers durable outcomes as shown by studies with a follow-up of 8-22 years. There are no similar data on durability for any other surgical treatment for BPO [247]. One study with a mean follow-up of thirteen years reported a significant and sustained decrease in most symptoms and improvement in urodynamic parameters. Failures were associated with DUA rather than re-development of BPO [92].

Online supplementary Table S.24 presents RCTs comparing TUIP with TURP [248-255]. A meta-analysis of short- and long-term data from ten RCTs found similar LUTS improvements and lower but insignificant improvements in Q_{max} for TUIP [250]. In this meta-analysis, an upper limit of prostate size was reported as an entry criterion for eight studies with five < 30 mL and three < 60 mL.

A second prostatic operation, usually re-TURP, has been reported at a constant annual rate of approximately 1-2%. A review analysing 29 RCTs found a retreatment rate of 2.6% after a mean follow-up of sixteen months [256]. In a large-scale study of 20,671 men, the overall retreatment rates (re-TURP, urethrotomy and bladder neck incision) were 5.8%, 12.3%, and 14.7%, at one, five, and eight years follow-up, respectively, and the respective incidence of re-TURP was 2.9%, 5.8% and 7.4% [257]. A meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after TURP (7.2%) [250].

Tolerability and safety: Peri-operative mortality and morbidity have decreased over time, but the latter remains considerable (0.1% and 11.1%, respectively) [258]. The possibility of increased long-term mortality compared to open surgery [259] has not been verified [260-262]. Data from 20,671 TURPs and 2,452 open prostatectomies (OP) showed that short- and long-term procedural mortality was similar (0.7% vs. 0.9% at 90 days, 2.8% vs. 2.7% at one year, 12.7% vs. 11.8% at five years, 20% vs. 20.9% at eight years) and that the eight year myocardial infarction rates were identical (4.8% vs. 4.9%) [257].

The risk of TUR-syndrome decreased to < 1.1% [256, 263]. No case has been recorded after TUIP. Data from 10,654 TURPs reported bleeding requiring transfusion in 2.9% [258]. The risk after TUIP is negligible. Similar results for TURP complications were reported by an analysis of contemporary RCTs using TURP as a comparator: bleeding requiring transfusion 2% (0-9%), TUR-syndrome 0.8% (0-5%), AUR 4.5% (0-13.3%), clot retention 4.9% (0-39%), and UTI 4.1% (0-22%) [246]. Long-term complications comprise urinary incontinence (1.8% after TUIP vs. 2.2% after TURP), urinary retention and UTIs, bladder neck contracture (BNC) (4.7% after TURP), urethral stricture (3.8% after TURP vs. 4.1% after TUIP), retrograde ejaculation (65.4% after TURP vs. 18.2% after TUIP), and ED (6.5% after TURP) [256].

Practical considerations: TURP and TUIP are effective treatments for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and TURP, respectively). No studies on the optimal cut-off value exist but the complication rates increase with prostate size [258]. The upper limit for TURP is suggested as 80 mL (based on Panel expert opinion, under the assumption that this limit depends on the surgeon's experience, resection speed, and choice of resectoscope size).

5.3.1.1 Modifications of TURP: bipolar TURP

Mechanism of action: Bipolar TURP (B-TURP) addresses a major limitation of monopolar TURP (M-TURP) by allowing performance in normal saline. Contrary to M-TURP, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed locally; energy is confined between an active (resection loop) and a passive pole situated on the resectoscope tip ("true" bipolar systems) or the sheath ("quasi" bipolar systems). Prostatic tissue removal is identical to M-TURP; however, B-TURP requires less energy/voltage because there is a smaller amount of interpolated tissue. Energy from the loop is transmitted to the saline solution, resulting in excitation of sodium ions to form plasma; molecules are then easily cleaved under relatively low voltage enabling resection. During coagulation, heat dissipates within vessel walls, creating a sealing coagulum and collagen shrinkage. The various bipolar devices available differ in the way in which current flow is delivered [264, 265].

Efficacy: Bipolar TURP is the most widely and thoroughly investigated alternative to M-TURP. Results from > 40 RCTs [266] have been reported, of which around half have been pooled in RCT-based meta-analyses [246, 267-270]. Early pooled results concluded that no clinically relevant differences exist in short-term (up to twelve months) efficacy (IPSS, QoL score and Q_{max}) [268]. Subsequent meta-analyses supported these conclusions [246, 267, 269, 270], though trial quality was generally poor. Data from RCTs with a follow-up of 12-60 months show no differences in efficacy parameters (online supplementary Table S.25) [271-277].

A meta-analysis has been recently conducted to specifically evaluate the quasi-bipolar Transurethral Resection in Saline (TURis, Olympus Medical) system vs. M-TURP, (<http://www.nice.org.uk/guidance/mtg23/>

[resources/the-turis-system-for-transurethral-resection-of-the-prostate-64371933166021](http://www.nice.org.uk/guidance/mtg23/resources/the-turis-system-for-transurethral-resection-of-the-prostate-64371933166021)). Ten unique RCTs (1,870 patients) were included. It was concluded that TURis was of equivalent efficacy to M-TURP.

Tolerability and safety: Early pooled results concluded that no differences exist in short-term (up to twelve months) urethral stricture/BNC rates, but B-TURP is preferable due to a more favourable peri-operative safety profile (elimination of TUR-syndrome; lower clot retention/blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [268]. Subsequent meta-analyses supported these conclusions [246, 267, 269, 270]. However, trial quality was relatively poor and limited follow-up might cause under-reporting of late complications, such as urethral stricture/BNC [268]. Data from individual RCTs with a follow-up of 12-60 months showed no differences in urethral stricture/BNC rates [270] (online supplementary Table S.25). However, in a recent RCT, a significantly higher stricture (urethral stricture + BNC) rate was detected for the first time in the B-TURP arm [278]. In this trial, 136 patients were randomised 1:1 to B-TURP (TURis) or M-TURP arm and followed up for 36 months. The primary endpoint was safety, including long-term complications such as strictures (urethral stricture + BNC). A significant difference in stricture rates favouring M-TURP was detected (6.6% vs. 19.0%). When patients were stratified according to prostate volume, no difference was detected in stricture rates between the arms in those with a prostate volume of up to 70 mL (TURis 3/40 [7.5%] vs. M-TURP: 3/39 [7.7%]; $P = 1.00$). However, in patients with prostate volume > 70 mL, a significantly higher stricture rate was seen in those submitted to TURis (9/23 [39.1%] vs. 1/22 [4.6%]; $P = 0.01$). Furthermore, in another RCT, a significantly higher BNC (but not urethral stricture) rate was detected for the first time in the B-TURP arm [279]. In this trial 137 patients were randomised 1:1 to B-TURP (performed with a “true” bipolar system [Gyrus PK SuperPulse, Olympus Medical]) or M-TURP arm and followed up to twelve months [279]. A significant difference in BNC rates favouring M-TURP was detected (0.0% vs. 8.5%; $P=0.02$), reinforcing a previously expressed potential association of BNC formation with the extremely focused electrical activity of a “true” bipolar system at the prostate level and thus, in close proximity to the bladder neck [276].

A RCT using the erectile function domain of the IIEF (IIEF-ED) showed that M-TURP and B-TURP have a similar effect on erectile function [280]. A comparative evaluation of the effects on overall sexual function, quantified with IIEF-15, showed no differences between B-TURP and M-TURP at twelve months follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [281].

A meta-analysis (<http://www.nice.org.uk/guidance/mtg23/resources/the-turis-system-for-transurethral-resection-of-the-prostate-64371933166021>) has shown that TURis reduces the risk of TUR-syndrome and the need for blood transfusion compared to M-TURP. It is plausible that TURis reduces length of hospital stay and re-admissions after surgery, although the evidence on these outcomes is limited.

Practical considerations: B-TURP offers an attractive alternative to M-TURP in patients with moderate-to-severe LUTS secondary to BPO, with similar efficacy but lower peri-operative morbidity [268]. The duration of improvements with B-TURP were documented in a number of RCTs with a follow-up of greater than twelve months. Mid-term results (up to five years) for B-TURP showed that safety and efficacy are comparable to M-TURP. The choice of B-TURP should be based on equipment availability, surgeon’s experience, and patient’s preference.

Recommendations	LE	GR
Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe.	1a	A
Offer bipolar- or monopolar- transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	1a	A

5.3.2 Open prostatectomy

Mechanism of action: Open prostatectomy is the oldest surgical treatment for moderate-to-severe LUTS secondary to BPO. Obstructive adenomas are enucleated using the index finger, approaching from within the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure). It is used for substantially enlarged glands (> 80-100 mL).

Efficacy: A few RCTs showed that holmium laser enucleation of the prostate (HoLEP), photoselective vaporisation of the prostate (PVP) and more recently, enucleation of the prostate using bipolar circuitry lead to similar outcomes compared to OP in men with large glands at a significantly lower complication rate [282-289]. Open prostatectomy reduces LUTS by 63-86% (12.5-23.3 IPSS points), improves QoL score by 60-87%, increases mean Q_{max} by 375% (+16.5-20.2 mL/s), and reduces PVR by 86-98% [282-284, 290, 291]. Efficacy is maintained for up to six years [292].

Two RCT-based meta-analysis evaluated the overall efficacy of endoscopic enucleation of the

prostate (EEP) vs. OP for treating patients with large glands [293, 294]. The larger study included RCTs involving 758 patients. Five RCTs compared OP with HoLEP [282, 283, 287] and four RCTs compared OP with EEP using bipolar circuitry [272-274, 278]. Open prostatectomy was performed via a transvesical approach in all RCTs. At 3-, 6-, 12- and 24-month follow-up, there were no significant differences in Q_{max} between EEP and OP. Post-void residual, PSA, IPSS and QoL score also showed no significant difference at 1-, 3-, 6- and 12-months. Furthermore, IIEF also showed no significant difference at 3-, 6- and 12- months. It was concluded that EEP appears to be an effective minimally invasive option for treating large prostates.

Tolerability and safety: Open prostatectomy mortality has decreased significantly during the past two decades (< 0.25%) [291]. The estimated transfusion rate is about 7-14% [282, 290, 291, 293]. Long-term complications include transient urinary incontinence (up to 10%), BNC and urethral stricture (about 6%) [282-284, 293, 295].

Two recent RCT-based meta-analysis evaluated the overall safety of EEP vs. OP for treating patients with large glands [293, 294]. Operation time was significantly longer for EEP, due to a significantly longer operation time needed for HoLEP (no difference was detected between OP and EEP using bipolar circuitry). Catheterisation and hospitalisation time was significantly shorter with EEP whilst IIEF-5 showed no significant difference between OP and EEP at twelve months [283, 286, 294]. Endoscopic enucleation of the prostate was also associated with fewer blood transfusions but there were no significant differences regarding other complications. It was concluded that EEP appears to be a minimally invasive option for treating large prostates.

Practical considerations: Open prostatectomy is the most invasive surgical method but it is an effective and durable procedure for the treatment of LUTS/BPO. Endoscopic enucleation techniques require experience and relevant endoscopic skills. In the absence of an endourological armamentarium including a holmium laser or a bipolar system, OP is the surgical treatment of choice for men with prostates > 80 mL.

Recommendation	LE	GR
Offer endoscopic enucleation of the prostate or open prostatectomy to treat moderate-to-severe LUTS in men with prostate size > 80 mL.	1a	A

5.3.3 Transurethral microwave therapy (TUMT)

Mechanism of action: Microwave thermotherapy works by emitting microwave radiation through an intraurethral antenna that delivers heat into the prostate. Tissue is destroyed (coagulation necrosis) by being heated at temperatures above cytotoxic thresholds (> 45°C). The heat may also cause apoptosis and denervation of α -receptors, thereby decreasing the smooth muscle tone of the prostatic urethra.

Efficacy: A systematic review and meta-analysis assessed therapeutic efficacy in different devices/software, including Prostatron (Prostasoft 2.0 and 2.5) and ProstaLund Feedback (online supplementary Table S.27) [281]. Symptom score after TUMT decreased by 65% in twelve months, compared to 77% after TURP. Transurethral resection of the prostate also achieved greater improvement in Q_{max} (119% vs. 70%) [296].

In one pooled analysis of three studies (two RCTs and one cohort study), with a twelve month follow-up, responder rate was 85.3% for ProstaLund Feedback TUMT (PLFT) and 85.9% for TURP [297]. The IPSS showed a subjective, non-inferior improvement with PLFT [297]. However, although both PLFT and TURP improved Q_{max} significantly, PLFT was inferior.

Previously, urinary retention was considered a contraindication for TUMT. Nowadays, LE:2b studies have reported a 77-93% short-term success rate for TUMT, defined as the percentage of patients who regained their ability to void spontaneously [298-301]. In one study with longer follow-up, cumulative retreatment risk at five years was estimated to be 42% for those without retention and 59% for those with retention at the baseline [302].

An RCT-based systematic review [296] (though the trials had different follow-up periods) found that TUMT patients (7.54/100 person-years) were more likely than TURP patients (1.05/100 person-years) to require retreatment for symptoms.

In a multicentre RCT with a five year follow-up, no significant differences were found in Q_{max} and IPSS between TUMT (PLFT; the Core-Therm device) and TURP. Additional treatment was needed in 10% after TUMT and in 4.3% after TURP. However, one must be cautious when interpreting these data because there was substantial loss to follow-up; less than half of the patients were analysed at four to five years. In addition, patients who remained in the study were likely to represent the best data (responders).

Tolerability and safety: Treatment is well tolerated, although most patients experience perineal discomfort and urinary urgency, and require pain medication for therapy. Pooled morbidity data comparing TUMT and TURP have been published [296, 297, 303]. In the Cochrane review of RCTs, catheterisation time, dysuria/urgency

and urinary retention rates were significantly smaller with TURP. On the other hand, hospitalisation time, haematuria, clot retention, transfusion, TUR-syndrome, sexual dysfunction and retreatment rates for urethral stricture/BNC were significantly smaller for TUMT [296].

Practical considerations: Endoscopy prior to TUMT is essential to identify the presence of a prostate middle lobe or an insufficient length of the prostatic urethra. Due to the low peri- and post-operative morbidity and lack of need for anaesthesia, TUMT is a true outpatient procedure and an option for (elderly) patients with comorbidities or greater anaesthesia risks [304].

Recommendations	LE	GR
Transurethral microwave therapy achieves symptom improvement comparable with, transurethral resection of the prostate (TURP) but transurethral microwave therapy is associated with decreased morbidity and lower flow improvements.	1a	A
Durability is in favour of TURP which has lower retreatment rates compared to transurethral microwave therapy.	1a	A

5.3.4 **Transurethral needle ablation of the prostate**

Mechanism of action: The transurethral needle ablation (TUNA™) device delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the parenchyma under direct vision using an attachment to the standard cystoscope. The energy induces coagulation necrosis in the transition zone resulting in reduction of prostate volume and BPO.

Efficacy: A meta-analysis of two RCTs, two non-randomised comparative and ten single-arm studies showed that TUNA™ achieved a 50% decrease in IPSS and a 70% improvement in Q_{max} at one year [305]. These findings are supported by a more recent meta-analysis of 35 studies (9 comparative, 26 non-comparative) [306]. Transurethral needle ablation of the prostate significantly improved IPSS and Q_{max} , but compared to TURP these improvements were significantly lower at twelve months. Mean differences in TURP vs. TUNA™ were 4.7 for IPSS and 5.9 mL/s for Q_{max} [306].

Clinical studies on the impact of TUNA™ on BPO [307, 308] showed a significant decrease in maximum detrusor pressure or detrusor pressure at Q_{max} . However, one out of six patients were still obstructed at one year [307].

The overall retreatment rate after TUNA™ was 19% based on an analysis of seventeen non-comparative studies (median follow-up unreported; only three out of seventeen studies had follow-up exceeding two years [306]); a rate considerably higher than that seen with TURP.

Tolerability and safety: Transient urinary retention and storage LUTS are common for weeks post-operatively [309, 310]. Generally, TUNA™ is associated with fewer adverse events compared to TURP, including mild haematuria, UTIs, strictures, incontinence, ED, and ejaculation disorders [305].

Practical considerations: Transurethral needle ablation of the prostate can be performed as a day-case procedure under local anaesthesia or sedation [309]. However, TUNA™ is not suitable for prostates > 75 mL or isolated bladder neck obstruction. In addition, TUNA™ cannot effectively treat prostatic middle lobes. There are also concerns about the durability of the effects achieved by TUNA™.

Recommendations	LE	GR
Transurethral needle ablation is a minimally invasive alternative with decreased morbidity compared to transurethral resection of the prostate (TURP) but with less efficacy	1a	A
Durability is in favour of TURP with lower retreatment rates compared to transurethral needle ablation.	1a	A

5.3.5 **Laser treatments of the prostate**

5.3.5.1 *Holmium laser enucleation and holmium laser resection of the prostate*

Mechanism of action: The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2,140 nm) is a pulsed solid-state laser that is absorbed by water and water-containing tissues. Tissue coagulation and necrosis are limited to 3-4 mm, which is enough to obtain adequate haemostasis [311]. Holmium laser resection of the prostate (HoLRP) or holmium laser enucleation of the prostate (HoLEP) result in BPO relief and, secondarily, in LUTS reduction.

Efficacy: In a meta-analysis of studies comparing HoLRP with TURP, no difference in symptom improvement could be detected at six or twelve months post-operatively (online supplementary Table S.29) [312]. One RCT comparing TURP with HoLRP with a minimum follow-up of four years showed no difference in urodynamics after 48 months [313]. Three meta-analyses covering trials on HoLEP vs. TURP found that symptom improvement was comparable or superior with HoLEP (online supplementary Table S.29) [314-316]. One RCT comparing photoselective vaporisation of the prostate (PVP) and HoLEP in patients with prostates > 60 mL showed comparable symptom improvement but significantly higher flow rates and lower PVR volume after HoLEP [317]. Another RCT on HoLAP and 80-W PVP showed comparable functional improvement within a median follow-up of 71 months [318].

RCTs indicate that HoLEP is as effective as OP for improving micturition in large prostates [282, 283], with similar re-operation rates after five years (5% vs. 6.7%, respectively) [282]. One RCT comparing HoLEP with TURP in a small number of patients with a seven year follow-up found that the functional long term results of HoLEP were comparable with TURP [319]. A retrospective study of HoLEP with the longest follow-up of up to ten years (mean 62 months) reported durable functional results with low re-operation rates [320].

Tolerability and safety: Dysuria is the most common post-operative complication [311, 314]. Compared to TURP, HoLRP has shorter catheterisation and hospitalisation times [312, 321]. Potency, continence, and major morbidity at 48 months were identical between HoLRP and TURP [313]. Three meta-analyses found that HoLEP has shorter catheterisation time and hospital stay, reduced blood loss, and fewer blood transfusions, but a longer operation time compared with TURP [314-316]. In a meta-analysis, no significant differences were noted between HoLEP and TURP for urethral stricture (2.6% vs. 4.4%), stress urinary incontinence (1.5% vs. 1.5%), and re-intervention (4.3% vs. 8.8%) [300]. HoLEP is superior to OP for blood loss, catheterisation and hospitalisation time [282, 283].

HoLEP has been safely performed in patients using anticoagulant medications [322, 323]. In a study of 83 patients, blood transfusion was required in seven patients (8%) [324]. A retrospective study compared the safety results of HoLEP in 39 patients who were on anticoagulant therapy at the time of their surgery, and 37 controls [323]. No transfusions were required and bleeding complication rates were not significantly different [323]. Short-term studies showed that patients with urinary retention could be treated with HoLEP [325, 326].

The impact on erectile function and retrograde ejaculation is comparable between HoLEP and TURP/OP [283, 327]. Erectile function did not decrease from baseline in either group; three quarters of sexually active patients had retrograde ejaculation after HoLEP.

Practical considerations: Holmium laser operations are surgical procedures that require experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications [322, 328].

5.3.5.2 532 nm ('Greenlight') laser vaporisation of prostate

Mechanism of action: The Kalium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. Laser energy is absorbed by haemoglobin, but not by water. Vaporisation leads to immediate removal of prostatic tissue, relief of BPO, and reduction of LUTS. In 2016 the standard Greenlight procedure was the 180-W-XPS laser, but the majority of evidence is published with the former 80-W (KTP) or 120-W HPS (LBO) laser systems. These three "Greenlight" laser systems differ not only in maximum power output, but more significantly in fibre design and the associated energy tissue interaction of each.

Efficacy: A meta-analysis of the nine available RCTs comparing PVP using the 80-W and 120-W lasers with TURP was performed in 2012 (online supplementary Table S.29) [329]. No differences were found in Q_{\max} and IPSS between 80-W-PVP and TURP, but only three RCTs provided sufficient twelve month data to be included in the meta-analysis [330-332]. With the 180-W (XPS) laser efficacy is comparable to TURP in terms of IPSS, Q_{\max} , PVR volume, prostate volume reduction, PSA decrease and QoL questionnaires. The XPS laser prostatectomy is superior to TURP in terms of catheterisation time, length of hospital stay and time to stable health status.

The longest RCT using the 80-W KTP laser has a follow-up of only twelve months [330]. A case series showed durable functional outcomes with the 80-W KTP laser, with an overall retreatment rate of 8.9% at five years [333]. Another case series of 500 patients treated with the 80-W system with a mean follow-up of 30.6 months reported a retreatment rate of 14.8% [334]. At twelve months self-reported urinary incontinence was 2.9% with XPS and 3.0% with TURP. Surgical re-intervention was comparably low after twelve months for both XPS and TURP.

Significant improvements in voiding parameters at a follow-up of twelve months were demonstrated urodynamically [335]. The longest RCT comparing the 120-W HPS laser with TURP had a follow-up of 36 months and showed a comparable improvement in IPSS, Q_{\max} , and PVR [336]. The re-operation rate was

higher after PVP (11% vs. 1.8%; $p = 0.04$) [336]. Similar improvement of IPSS, QoL, Q_{max} , or urodynamic parameters was reported from two RCTs with a maximum follow-up of 24 months [331, 337].

A multicentre case series of the 180-W laser demonstrated comparable safety and symptom improvement for the 180-W laser and the former Greenlight laser systems [338].

Tolerability and safety: A meta-analysis of the RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time but shorter catheterisation time and length of hospital stay after PVP [329]. Blood transfusions and clot retention were less with PVP. No difference was noted in post-operative urinary retention, infection, meatal stenosis, urethral stricture, or bladder neck stenosis [329]. According to the Goliath Study, 180-W Greenlight laser prostatectomy is non-inferior to TURP in terms of peri-operative complications, including post-operative dysuria rate (XPS 19.1%;TURP 21.8%). Post-operative Clavien III re-interventions are more likely within the first 30 days after TURP compared to XPS (3.8% vs. 9.8%; $p = 0.04$), but comparable after twelve months follow-up. There are more severe bleeding complications within 30 days after TURP and more mild bleeding complications after XPS laser prostatectomy over twelve months, leading to a comparable overall incidence between both techniques.

The Greenlight laser appears to be safe in high-risk patients under anticoagulation treatment [339-343]. In one study, anticoagulant patients had significantly higher rates of bladder irrigation (17.2%) compared with those not taking anticoagulants (5.4%) [342]. Safety in patients with urinary retention, or prostates > 80 mL was shown in various prospective non-randomised trials [343-345].

The impact of Greenlight laser on sexual function and abnormal ejaculation was similar to that of TURP after twelve months [346]. In addition, no difference was reported between OP/TURP and Greenlight PVP for erectile function [347, 348], IIEF-5 scores are maintained after treatment. However, in patients with pre-operative IIEF-5 > 19, the post-operative IIEF-5 scores were significantly decreased at 6, 12, and 24 months [349].

Practical considerations: The 180-W XPS laser should be regarded as the reference for Greenlight laser prostatectomy. However, many former studies were done with the out-dated 80-W and 120-W lasers therefore, results need to be interpreted accordingly. Long-term results from the Goliath Study (180-W XPS vs. TURP) are pending. The intermediate two year follow-up data showed efficacy and safety outcomes similar to TURP [350].

5.3.5.3 Diode laser vaporisation of the prostate

Mechanism of action: For prostate surgery, diode lasers with a wavelength of 940, 980, 1,318, and 1,470 nm (depending on the semiconductor used) are marketed for vaporisation and enucleation. Only a few have been evaluated in clinical trials [351].

Efficacy: Case series, and two comparative studies of vaporisation using a 980 nm diode laser or a 120-W HPS laser, are available [352-358]. Quality of life, IPSS, Q_{max} , and PVR improved significantly in all studies compared to baseline and were similar for both laser, at six and twelve months [352, 353].

One RCT with a twelve month follow-up compared the 980 nm diode laser with bipolar enucleation and found equal clinical outcome [359]. One small RCT with a six month follow-up comparing laser enucleation using a 1,318 nm diode laser with B-TURP reported similar efficacy (online supplementary Table S.29) [360]. This data is further supported by one RCT, comparing 980 nm diode laser vaporisation vs. TURP within a two year follow-up [361]. Redo TURP was more frequent in the diode laser group (online supplementary Table S.29) [359].

Tolerability and safety: Published studies on 980 nm laser vaporisation indicate high haemostatic potential, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% of patients, respectively [352, 353]. Post-operatively, a high rate of dysuria was reported [352-354, 361]. Fibre modifications led to a significant reduction in surgical time [355]. Furthermore, the literature on diode vaporisation reports high re-operation rates (8-33%) and persisting stress urinary incontinence (9.1%) [352-354, 361]. In contrast, the two RCTs on diode laser enucleation showed that blood loss, hospitalisation and catheterisation time were in favour of diode laser enucleation, with equivalent clinical outcome for either bipolar enucleation [359] or TURP [360] during follow-up.

Practical considerations: Diode laser vaporisation leads to immediate improvement of LUTS due to BPO and provides good haemostatic properties. Diode laser enucleation seems to offer similar efficacy and safety when compared to either TURP or bipolar enucleation. Based on the limited number, mainly low quality RCTs and controversial data on the retreatment rate, results for diode laser vaporisation should be evaluated in further higher quality RCTs.

5.3.5.4 Thulium:yttrium-aluminium-garnet laser (Tm:YAG)

Mechanism of action: In the Tm:YAG laser, a wavelength between 1,940 and 2,013 nm is emitted in continuous wave mode. The laser is primarily used in front-fire applications [351, 362]. Different applications, ranging from vaporisation (ThuVaP), vaporessection (ThuVaRP), and enucleation (ThuVEP/ThuLEP: similar enucleating techniques) are published.

Efficacy: One RCT with a four year follow-up comparing ThuVARP to M-TURP, showed comparable efficacy and favourable re-operation rates in the ThuVaRP group [363] (online supplementary Table S.29). One RCT and one non-RCT compared ThuVaRP with M-TURP [364, 365], while two RCTs comparing ThuVaRP and B-TURP were published recently [366, 367]. In summary, studies show comparable improvement of symptoms and voiding parameters. There are only a few case studies on ThuVEP showing a significant improvement in IPSS, Q_{max} , and PVR after treatment [368-371]. ThuLEP and HoLEP were compared in one RCT with eighteen months follow-up with comparable outcomes in both arms (online supplementary Table S.29) [356]. Furthermore, ThuLEP and bipolar enucleation were compared in one RCT with twelve months follow-up. The outcome showed no difference with regard to efficacy whilst the decrease in hemoglobin level and catheter time were significantly lower for ThuLEP [372].

Tolerability and safety: Thulium laser prostatectomy shows high intra-operative safety in RCTs [363, 364], as well as in case series in patients with large prostates [368] and anticoagulation or bleeding disorders [369, 373]. Catheterisation time, hospital stay, and blood loss were shorter compared to TURP [364-366]. The rate of post-operative urethral strictures after ThuVaRP was 1.9%, the rate of bladder neck contracture was 1.8%, and the re-operation rate was 0-7.1% during follow-up [364, 365, 374]. Urethral stricture after ThuVEP occurred in 1.6%, and the overall retreatment rate was 3.4% (mean follow-up 16.5 months) [375]. No urethral and bladder neck strictures after ThuLEP were reported during the eighteen months follow-up [376]. Recently, a study focused on post-operative complications after ThuVEP (vapoenucleation) reported adverse events in 31% of cases, with 6.6% complications greater than Clavien grade II [377]. One case control study on ThuVEP with 48-month follow-up reported long-term durability of voiding improvements and overall re-operation rates of 2.4% [373]. Two studies (one case control, one RCT vs. TURP) addressed the impact of ThuVEP on sexual function, demonstrating no effect on erectile function with increased prevalence of retrograde ejaculation post-operatively [378, 379].

A prospective multicentre study on ThuVARP, including 2,216 patients, showed durable post-operative improvement in IPSS, QoL, Q_{max} , and PVR for the entire eight years of follow-up. Urethral stricture and bladder neck contracture accounted for 2.6 % and 1.6 % of patients, respectively. Persistent stress incontinence was found in 0.1 % whilst, re-operation due to BPH recurrence was required in 1.2 % patients [380].

In two RCTs on ThuLEP versus TURP, one RCT on ThuLEP versus bipolar enucleation and one RCT on ThuLEP versus HoLEP, ThuLEP appeared to be equivalent with regard to clinical efficacy and superior with regard to intra-operative haemostasis. The same was demonstrated for ThuVEP vs. TURP in one RCT [381].

Practical considerations: The limited number of RCTs and only a few studies with long-term follow-up (up to 48 months) support the efficacy of thulium laser prostatectomy therefore, there is a need for ongoing confirmation.

Recommendations	LE	GR
Holmium laser enucleation and 532-nm laser vaporisation of the prostate are alternatives to transurethral resection of the prostate (TURP) in men with moderate-to-severe LUTS leading to immediate, objective, and subjective improvements comparable with TURP.	1a	A
The short-term and mid-term functional results of 532-nm laser vaporisation of the prostate are comparable with TURP.	1b	A
The long-term functional results of holmium laser enucleation are comparable with TURP or open prostatectomy.	1b	A
Thulium enucleation may be an alternative to TURP and holmium laser enucleation in men with moderate-to-severe LUTS leading to immediate and mid-term objective and subjective improvements.	1b	A
Diode laser operations lead to short-term objective and subjective improvement.	1b	B
Tm:YAG vaporessection is an alternative to TURP for small- and medium-size prostates.	1b	A
With regard to intra-operative safety and haemostatic properties, diode and thulium lasers appear to be safe.	3	C
With regard to intra-operative safety, 532-nm laser vaporisation is superior to TURP.	1b	A
532-nm laser vaporisation should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.	3	B

5.3.6 Prostatic stents

Mechanism of action: The use of an endoprosthesis to preserve luminal patency is a well-established concept. Prostatic stents were primarily designed as an alternative to an indwelling catheter but have also been assessed as a primary treatment option in patients without significant comorbidities [382, 383].

A prostatic stent requires a functioning detrusor [384]. Permanent stents are biocompatible, allowing for epithelialisation. Temporary stents do not epithelialise and may be either biostable or biodegradable. Temporary stents can provide short-term relief from BPO in patients temporarily unfit for surgery, or after minimally invasive treatment [384].

Efficacy: Several small case studies on a range of stents of different designs and materials provide low level evidence for their use. Online supplementary Table S.30 describes the most important studies [382, 383, 385-388]. There was a substantial loss to follow-up in all studies. There are no studies comparing stents with sham or other treatment modalities, and only one RCT compared two versions of a prostatic stent for BPO [389].

The main representative of the permanent stents is the UroLume prosthesis. A systematic review identified 20 case series (990 patients), with differing follow-ups [390]. These studies reported relevant symptom improvement and Q_{max} increase [390]. The pooled data from studies with patients who were catheter dependent showed that 84% of patients (148/176) regained the ability to void spontaneously after UroLume treatment [390, 391].

The data on non-epithelialising prostatic stents was summarised in a systematic review on the efficacy of Memokath, a self-expanding metallic prostatic stent [392]. Overall, IPSS was reduced by 11-19 points and Q_{max} increased by 3-11 mL/s [392].

Tolerability and safety: In general, stents are subject to misplacement, migration, and poor tolerability because of exacerbation of LUTS and encrustation [384]. The most immediate and common adverse events include perineal pain or bladder storage symptoms.

Practical considerations: Due to common side effects and a high migration rate, prostatic stents have a limited role in the treatment of moderate-to-severe LUTS. Temporary stents can provide short-term relief from LUTS secondary to BPO in patients temporarily unfit for surgery or after minimally invasive treatment [384].

Recommendation	LE	GR
Offer prostatic stents as an alternative to catheterisation in men unfit for surgery.	3	C

5.3.7 Prostatic urethral lift

Mechanism of action: The prostatic urethral lift (PUL) represents a novel minimally invasive approach under local or general anaesthesia. Encroaching lateral lobes are compressed by small permanent suture-based implants delivered under cystoscopic guidance (Urolift®) resulting in an opening of the prostatic urethra that leaves a continuous anterior channel through the prostatic fossa ranging from the bladder neck to the verumontanum.

Efficacy: The available studies on PUL are presented in online supplementary Table S.31 [393-398]. In general, PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%). There is only one RCT comparing PUL with sham [393]. The primary endpoint was met at three months with a 50% reduction in AUA-SI from 22.1 to 11.0 points and remained stable up to twelve months. Change for AUA-SI was 88% greater for the treatment group than sham control. Also Q_{max} increased significantly from 8.1 to 12.4 mL/s relative to baseline at three months and this result could still be confirmed at twelve months. The difference in clinical response for Q_{max} between both groups was of statistical significance. A relevant benefit with regard to PVR was not demonstrated compared to baseline nor relative to sham control.

An RCT of 80 patients, conducted in nine European countries, comparing PUL to TURP was published in 2015. At twelve months, IPSS improvement was -11.4 for PUL and -15.4 for TURP. There was no retrograde ejaculation among PUL patients, while 40% of TURP patients lost the ability to ejaculate. Surgical recovery was measured using a validated instrument and confirmed that recovery from PUL is more rapid and more extensive in the first three to six months [399]. However, TURP resulted in much greater improvements in Q_{max} (+13.7 ± 10.4 mL/s) after twelve months compared to PUL. (4.0 ± 4.8 mL/s).

In a recent meta-analysis of retrospective and prospective trials, pooled estimates showed an overall improvement following PUL, including IPSS (-7.2 to -8.7 points), Q_{max} (3.8 to 4.0 mL/s), and QoL (-2.2 to -2.4 points) [398]. Sexual function was preserved with a small improvement estimated at twelve months.

A multi-centre, randomised and blinded trial of PUL in men with bothersome LUTS due to BPH showed that at three years, average improvements from baseline were significant for total IPSS (41.1%), QoL (48.8%), Q_{max} (53.1%) and individual IPSS symptoms. Symptomatic improvement was independent of prostate size. There were no *de novo*, sustained ejaculatory or erectile dysfunction events and all sexual function assessments showed average stability or improvement after PUL [400].

Tolerability and safety: The most common complications reported post-operatively included haematuria (16-63%), dysuria (25-58%), pelvic pain (5-17.9%), urgency (7.1-10%), transient incontinence (3.6-16%), and UTI (2.9-11%). Most symptoms were mild-to-moderate in severity and resolved within two to four weeks after the procedure.

Prostatic urethral lift seems to have no significant impact on sexual function. Evaluation of sexual function as measured by IIEF-5, Male Sexual Health Questionnaire-Ejaculatory Dysfunction, and Male Sexual Health Questionnaire-Bother in patients undergoing PUL showed that erectile and ejaculatory function were preserved [393-397].

Practical considerations: An obstructed/protruding median lobe cannot be effectively treated, and the effectiveness in large prostate glands has not been shown yet. Long-term studies are needed to evaluate the duration of the effect in comparison to other techniques.

Recommendation	LE	GR
Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe. Inform patients that long-term effects have not been evaluated.	1a	B

5.3.8 **Novel interventions**

5.3.8.1 *Intra-prostatic injections*

Mechanism of action: Various substances have been injected directly into the prostate in order to improve LUTS, these include Botulinum toxin-A (BoNT-A), NX-1207 and PRX302. The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons via cleavage of synaptosome-associated protein 25 (SNAP-25). However, BoNT-A also appears to act at various other levels by modulating the neurotransmissions of sympathetic, parasympathetic and sensory nerve terminals in the prostate, leading to a reduction in growth and apoptosis of the prostate [401]. The detailed mechanisms of action for the injectables NX-1207 and PRX302 are not completely understood, but experimental data associates apoptosis-induced atrophy of the prostate with both drugs [401].

Efficacy: Results from clinical trials have shown only modest clinical benefits, that do not seem to be superior to placebo, for BoNT-A [402, 403] (see online supplementary Table S.32). A recent systematic review and meta-analysis showed no differences in efficacy compared with placebo, and concluded that there is no evidence of clinical benefits in medical practice [404]. With regard to NX-1207 and PRX302, the positive results from Phase II-studies have not been confirmed in Phase III-trials thus far [405, 406].

Safety: Studies including safety assessments have reported only a few mild and self-limiting adverse events for all injectable drugs [401]. Furthermore, a recent systematic review and meta-analysis showed low incident rates of procedure-related adverse events [404].

Practical considerations: Although experimental evidence for compounds such as NX-1207, PRX302 and BoNT-A was promising for their transition to clinical use, randomised, controlled studies of all three of these injectable agents have not been able to reveal any significant clinical benefits.

Recommendation	LE	GR
Do not offer Botulinum toxin injection treatment to patients with male LUTS.	1a	B

5.3.8.2 Minimal invasive simple prostatectomy

Mechanism of action: The term minimal invasive simple prostatectomy (MISP) includes laparoscopic simple prostatectomy (LSP) and robot-assisted simple prostatectomy (RASP). The technique for LSP was first described in 2002 [407], while the first RASP was reported in 2008 [408]. Both LSP and RASP are performed using different personalised techniques, developed based on the transcapsular (Millin) or transvesical (Freyer) techniques of OP. An extraperitoneal approach is mostly used for LSP, while a transperitoneal approach is mostly used for RASP.

Efficacy: A recent systematic review and meta-analysis showed that in 27 observational studies including 764 patients, the mean increase in Q_{max} was 14.3 mL/s (95% CI 13.1-15.6), and the mean improvement in IPSS was 17.2 (95% CI 15.2-19.2). Mean duration of operation was 141 min (95% CI 124-159), and the mean intra-operative blood loss was 284 mL (95% CI 243-325). One hundred and four patients (13.6%) developed a surgical complication. In comparative studies to OP, length of hospital stay (WMD -1.6 days, $p = 0.02$), length of catheter use (WMD -1.3 days, $p = 0.04$) and estimated blood loss (WMD -187 mL, $p = 0.015$) were significantly lower in the MISP group, while the duration of operation was longer than in OP (WMD 37.8 min, $p < 0.0001$). There were no differences in improvements in Q_{max} , IPSS and peri-operative complications between both procedures (see online supplementary Table S.33).

Two recent retrospective series on RASP are now available which were not included in the meta-analysis which confirm these findings [409, 410]. The largest retrospective series reports 1,330 consecutive cases including 487 robotic (36.6%) and 843 laparoscopic (63.4%) simple prostatectomy cases. The authors confirm that both techniques can be safely and effectively done in selected centres [409]. Technical variations also include an intrafascial (IF) approach. Comparing laproscopic, robotic and robotic IF simple prostatectomy, the IF-RSP technique is safe and effective, with results at one year follow-up for continence, IPSS and Sexual Health Inventory for Men scores similar to those for the LSP and RSP techniques [411].

Tolerability and safety: In the largest series, the post-operative complication rate was 10.6% (7.1% for LSP and 16.6% for RASP), most of the complications being of low grade. The most common complications in the RASP series were hematuria requiring irrigation, UTI and AUR; in the LSP series, the most common complications were UTI, ileus and AUR.

Practical considerations: Data on MISP are increasing from selected centres. MISP seems comparable to OP in terms of efficacy and safety, providing similar improvements in Q_{max} and IPSS [412]. However, most studies are of a retrospective nature. High quality studies are needed to compare the efficacy, safety, and hospitalisation times of MISP and both OP and endoscopic methods. Long-term outcomes, learning curve and cost of MISP should also be evaluated.

Evidence Statement	LE
Minimal invasive simple prostatectomy seems to be feasible in men with prostate sizes > 80 mL needing surgical treatment; however, RCTs are needed.	2a

5.4 Patient selection

The choice of treatment depends on the assessed findings of patient evaluation, ability of the treatment to change the findings, treatment preferences of the individual patient, and the expectations to be met in terms of speed of onset, efficacy, side effects, QoL, and disease progression. Online supplementary Table S.34 provides differential information about speed of onset and influence on basic parameters of conservative, medical or surgical treatment options.

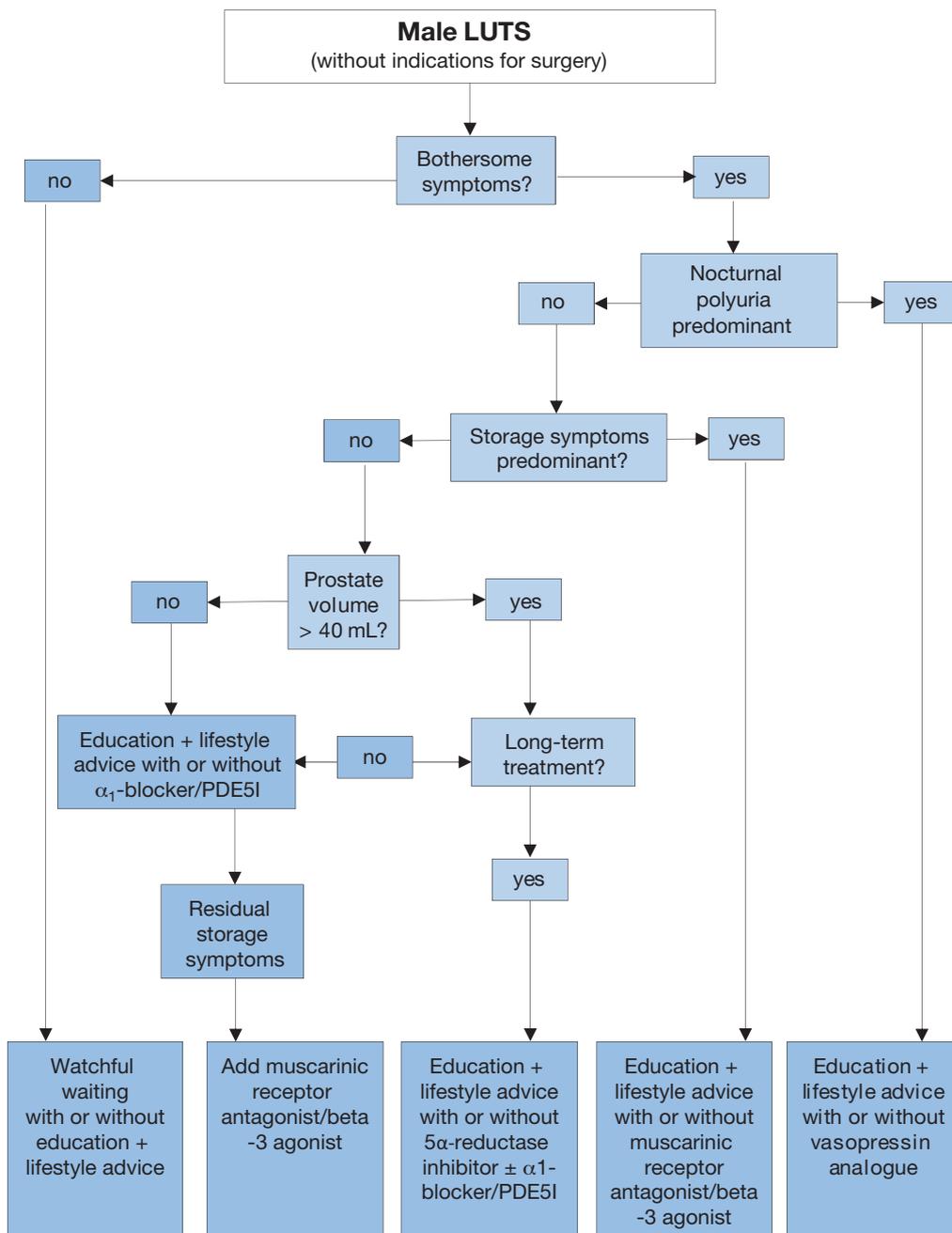
Behavioural modifications, with or without medical treatments, are usually the first choice of therapy.

Figure 3 provides a flow chart illustrating treatment choice according to evidence-based medicine and patient profiles.

Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery).

Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' preferences, willingness to accept surgery-associated specific side-effects, availability of the surgical armamentarium, and experience of the surgeon with these surgical techniques. An algorithm for surgical approaches according to evidence-based medicine and the patient's profile is provided in figure 4.

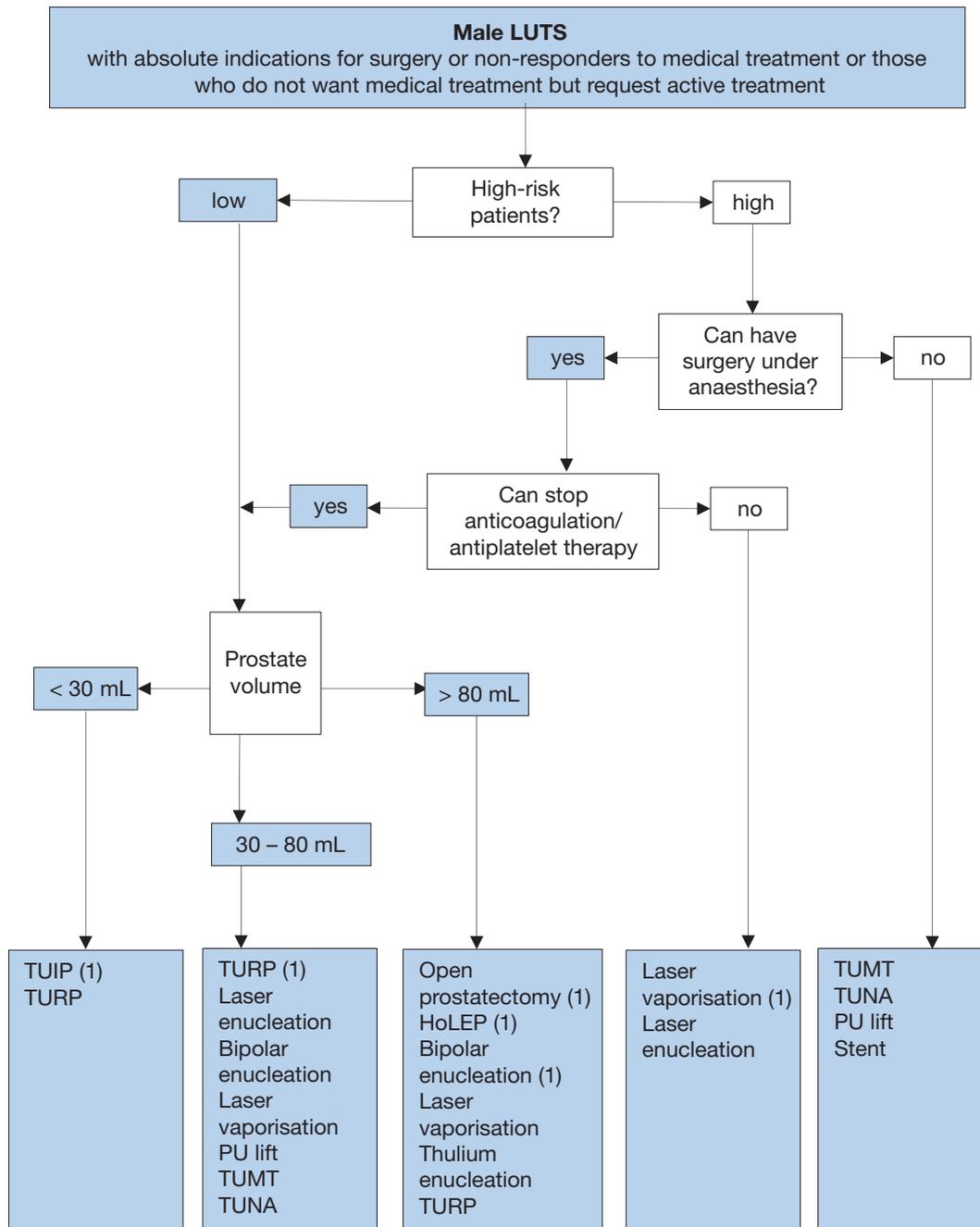
Figure 3: Treatment algorithm of male LUTS using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation. Note that patients' preferences may result in different treatment decisions.



LUTS = lower urinary tract symptoms; PDE5I = phosphodiesterase type 5 inhibitors.

Notice: Readers are strongly recommended to read the full text that highlights the current position of each treatment in detail.

Figure 4: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications. The flowchart was stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size.



(1) Current standard/first choice. The alternative treatments are presented in alphabetical order.
Notice: Readers are strongly recommended to read the full text that highlights the current position of each treatment in detail.

Laser vaporisation includes GreenLight, thulium, and diode lasers vaporisation;

Laser enucleation includes holmium and thulium laser enucleation.

HoLEP = holmium laser enucleation; TUIP = transurethral incision of the prostate; TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation; TURP = transurethral resection of the prostate.

5.5 Management of Nocturia in men with lower urinary tract symptoms

The following section reports a systematic review of therapy for the management of nocturia in men with LUTS. It also emphasises the need to consider the wide range of possible causes of nocturia. This summary

print version is supplemented by a detailed online version (<http://uroweb.org/guideline/treatment-of-non-neurogenic-maleluts/>).

Nocturia is defined as the complaint of waking at night to void [2]. It reflects the relationship between the amount of urine produced while asleep, and the ability of the bladder to store the urine received. Nocturia can occur as part of lower urinary tract dysfunction (LUTD), such as OAB and chronic pelvic pain syndrome. Nocturia can also occur in association with other forms of LUTD, such as BOO, but here it is debated whether the link is one of causation or simply the co-existence of two common conditions. Crucially, nocturia may have behavioural, sleep disturbance (primary or secondary) or systemic causes unrelated to LUTD (Table 1). Differing causes often co-exist and each has to be considered in all cases. Only where LUTD is contributory should nocturia be termed a LUTS.

Table 1: Categories of nocturia

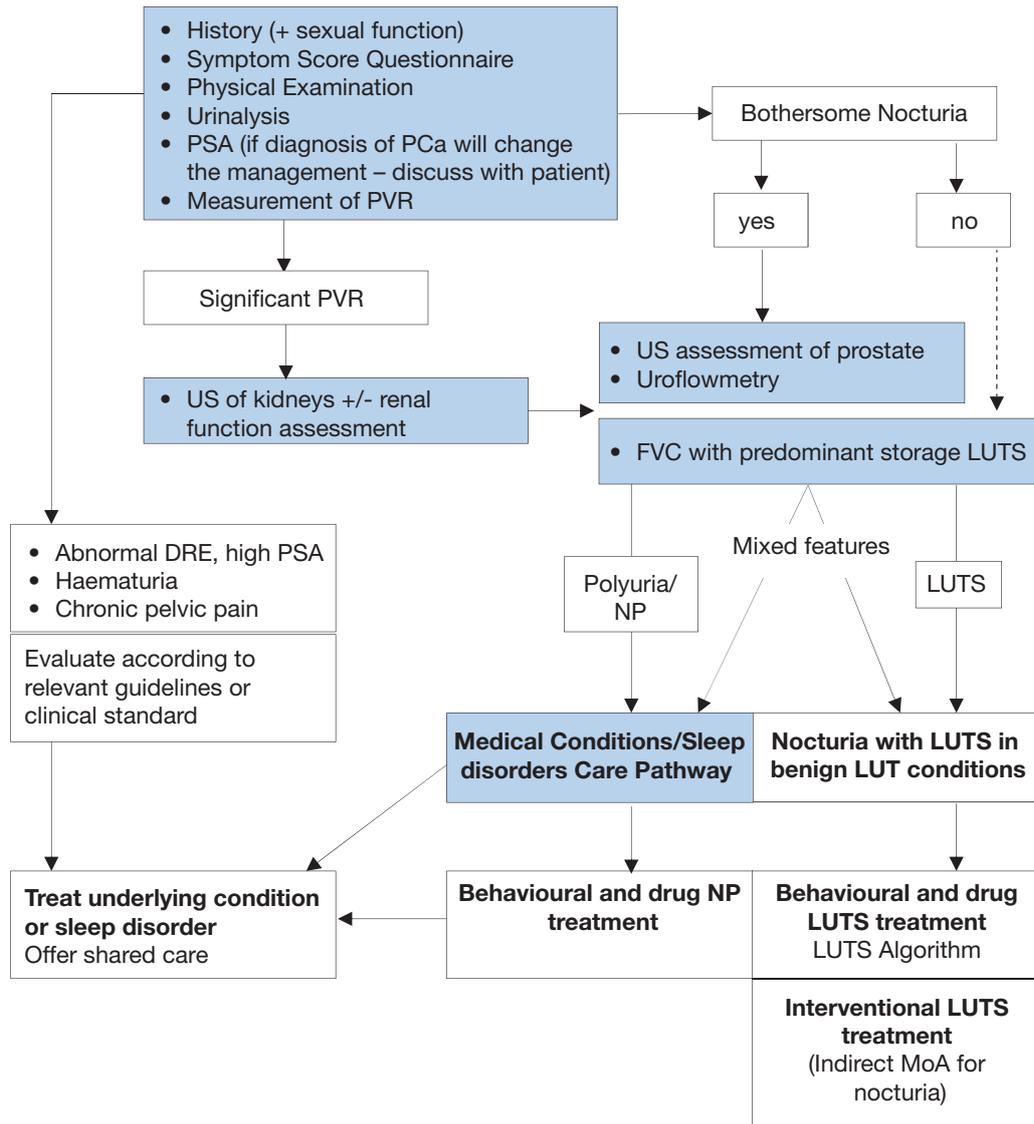
CATEGORY	Disproportionate urine production (at all times, or during sleep)	Low volume of each void (at all times, or overnight)
<i>Behavioural</i>	Inappropriate fluid intake	“Bladder awareness” due to secondary sleep disturbance
<i>Systemic</i>	Water, salt and metabolite output	
<i>Sleep disorder</i>	Variable water and salt output	“Bladder awareness” due to primary sleep disturbance
<i>LUTD</i>		Impaired storage function and increased filling sensation

5.5.1 **Diagnostic assessment**

Evaluation is outlined in Figure 5;

1. Evaluate for LUTD according to the relevant guidelines. The severity and both of individual LUTS should be identified with a symptom score, supplemented by directed questioning if needed. A validated bladder diary is mandatory.
2. Review whether behavioural factors affecting fluid balance and sleep are contributing.
3. Review of medical history and medications, including directed evaluation for key conditions, such as renal failure, diabetes mellitus, cardiac failure, and obstructive sleep apnoea. If systemic factors or sleep disorders are potentially important, consider involving appropriate medical expertise (see Figure 6). This is appropriate where a known condition is sub-optimally managed, or symptoms and signs suggest an undiagnosed condition.

Figure 5. Evaluation of Nocturia in non-neurogenic Male LUTS.



Assessment must establish whether the patient has polyuria, LUTS, sleep disorder or a combination. Therapy may be driven by the bother it causes, but non-bothersome nocturia may warrant assessment of a frequency volume chart (indicated by the dotted line) depending on history and clinical examination since potential presence of a serious underlying medical condition must be considered.

FVC = frequency volume chart; DRE = digital rectal examination; NP = nocturnal polyuria; MoA = mechanism of action; PVR = post-void residual.

5.5.2 Medical conditions and sleep disorders Shared Care Pathway

Causative categories for nocturia comprise [413]:

1. Bladder storage problems;
2. 24-hour (global) polyuria (> 40 mL/kg urine output over a 24-hour period);
3. Nocturnal polyuria (NP; nocturnal output exceeding 20% of 24-hour urine output in the young, or 33% of urine output in people > 65 [2]);
4. Sleep disorders;
5. Mixed aetiology.

Potentially relevant systemic conditions are those which impair physiological fluid balance, including influences on: levels of free water, salt, other solutes and plasma oncotic pressure; endocrine regulation e.g. by antidiuretic hormone (ADH), natriuretic peptides; cardiovascular and autonomic control; renal function; neurological regulation, e.g. circadian regulation of the pineal gland, and renal innervation. As nocturia is commonly referred to the specialty without full insight into cause, the urologist must review the likely mechanisms underlying a presentation with nocturia, and instigate review by relevant specialties accordingly. Thus, the managing urologist needs to evaluate nocturia patients in a context where additional medical

expertise is available (Figure 6). They should not proceed along any LUTD management pathway unless a causative link with LUTD is justifiably suspected, and systemic or sleep abnormalities have been considered.

In patients with non-bothersome nocturia, the medical evaluation (history and physical examination) should consider the possibility of early stages of systemic disease, and whether there is possibility of earlier diagnosis or therapy adjustment.

Some important potentially treatable non-urological causes of nocturia include; obstructive sleep apnoea (OSA), congestive cardiac failure, poorly controlled diabetes mellitus and medications (e.g. diuretics, or lithium).

Figure 6: Shared care pathway for nocturia, highlighting the need to manage potentially complex patients using relevant expertise for the causative factors.

UROLOGICAL CONTRIBUTION	SHARED CARE	MEDICAL CONTRIBUTION
Diagnosis of LUTD <ul style="list-style-type: none"> • Urological/LUTS evaluation • Nocturia symptom scores • Bladder diary 		Diagnosis of conditions causing NP <ul style="list-style-type: none"> • Evaluate patient's known conditions • Screening for sleep disorders • Screening for potential causes of polyuria*
Conservative management Behavioural therapy <ul style="list-style-type: none"> • Fluid/sleep habits advice • Drugs for storage LUTS • (Drugs for voiding LUTS) • ISC/catherisation 	Conservative management <ul style="list-style-type: none"> • Antidiuretic • Diuretics • Drugs to aid sleep 	Management <ul style="list-style-type: none"> • Initiation of therapy for new diagnosis • Optimised therapy of known conditions
Interventional therapy <ul style="list-style-type: none"> • Therapy of refractory storage LUTS • Therapy of refractory voiding LUTS 		* Potential causes of polyuria NEPHROLOGICAL DISEASE <ul style="list-style-type: none"> • Tubular dysfunction • Global renal dysfunction CARDIOVASCULAR DISEASE <ul style="list-style-type: none"> • Cardiac disease • Vascular disease ENDOCRINE DISEASE <ul style="list-style-type: none"> • Diabetes insipidus/mellitus • Hormones affecting diuresis/natriuresis NEUROLOGICAL DISEASE <ul style="list-style-type: none"> • Pituitary and renal innervation • Autonomic dysfunction RESPIRATORY DISEASE <ul style="list-style-type: none"> • Obstructive sleep apnoea BIOCHEMICAL <ul style="list-style-type: none"> • Altered blood oncotic pressure

5.5.3 Treatment for Nocturia

5.5.3.1 Antidiuretic therapy

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and control of urine production by binding to V2 receptors in the renal collecting ducts. Arginine vasopressin increases water re-absorption and urinary osmolality, so decreasing water excretion and total urine volume. Arginine vasopressin also has V1 receptor mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for treating nocturia/nocturnal polyuria.

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and no relevant V1 receptor affinity. It has been investigated for treating nocturia [414], with specific doses, titrated dosing, differing formulations, and options for route of administration. Antidiuretic therapy using desmopressin, with dose titration to achieve clinical response, is more effective than placebo in terms of reduced nocturnal voiding frequency and other outcome measures. Three studies evaluating titrated-dose desmopressin in which men were included, reported seven serious adverse events in 530 patients, with one death. There were seventeen cases of hyponatraemia and seven of hypertension. Headache was reported in 53 and nausea in fifteen.

Practical considerations

Desmopressin is taken once daily before sleeping. Because the optimal dose differs between patients, desmopressin treatment should be initiated at a low dose (0.1 mg/day) and may be gradually increased up to a dosage of 0.4 mg/day every week until maximum efficacy is reached. Patients should avoid drinking fluids at least one hour before and for eight hours after dosing. In men aged 65 years or older, desmopressin should not be used if the serum sodium concentration is below normal: all patients should be monitored for hyponatremia. Men with nocturia should be advised regarding off-label use.

5.5.3.2 Medications to treat LUTD

Where LUTD is diagnosed and considered causative of nocturia, relevant medications for storage (and voiding) LUTS may be considered. However, effect size of these medications is generally small, or not significantly different from placebo when used to treat nocturia. Applicable medications include; selective α 1-adrenergic antagonists [415], antimuscarinics [416-418], 5 α -reductase inhibitors [419] and PDE5Is [420].

5.5.3.3 Other medications

Diuretics, agents to promote sleep [421], diuretics [422], non-steroidal anti-inflammatory agents (NSAIDs) [423] and phytotherapy [424]. Effect size of these medications in nocturia is generally small, or not significantly different from placebo. Larger responses have been reported for some medications, but larger scale confirmatory RCTs are lacking. Agents to promote sleep do not appear to reduce nocturnal voiding frequency, but may help patients return to sleep.

Recommendations	LE	GR
Treatment should aim to address underlying causative factors, which may be behavioural, systemic condition(s), sleep disorders, lower urinary tract dysfunction, or a combination of factors.	4	A*
Discuss lifestyle changes to reduce nocturnal urine volume and episodes of nocturia, and improve sleep quality.	3	A*
Desmopressin may be prescribed to decrease nocturia due to nocturnal polyuria in men under the age of 65. Screening for hyponatremia must be undertaken at baseline, during dose titration and during treatment.	1a	A
α 1-adrenergic antagonists may be offered to men with nocturia associated with LUTS.	1b	B
Antimuscarinic drugs may be offered to men with nocturia associated with overactive bladder.	1b	B
5 α -reductase inhibitors may be offered to men with nocturia who have moderate-to-severe LUTS and an enlarged prostate (> 40 mL).	1b	C
Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia.	1b	B
A trial of timed diuretic therapy may be offered to men with nocturia due to nocturnal polyuria. Screening for hyponatremia should be undertaken at baseline and during treatment.	1b	C
Agents to promote sleep may be used to aid return to sleep in men with nocturia.	2	C

*Upgraded based on Panel consensus.

6. FOLLOW-UP

6.1 Watchful waiting (behavioural)

Patients who elect to pursue a WW policy should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, IPSS, uroflowmetry, and PVR volume.

6.2 Medical treatment

Patients receiving α 1-blockers, muscarinic receptor antagonists, beta-3 agonists, PDE5Is or the combination of α 1-blockers and 5-ARIs or muscarinic receptor antagonists should be reviewed four to six weeks after drug initiation to determine the treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, IPSS, uroflowmetry, and PVR volume. FVC or bladder diaries should be used to assess response to treatment for predominant storage symptoms or nocturnal polyuria.

Patients receiving 5-ARIs should be reviewed after twelve weeks and six months to determine their response and adverse events. The following are recommended at follow-up visits: history, IPSS, uroflowmetry and PVR volume.

Men taking 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is greater than ten years and if a diagnosis of PCa could alter management. A new baseline PSA should be determined at six months, and any confirmed increase in PSA while on 5-ARIs should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day three and seven as well as after one month, and if serum sodium concentration has remained normal, every three

months subsequently. The following tests are recommended at follow-up visits: serum-sodium concentration and frequency volume chart. The follow-up sequence should be restarted after dose escalation.

6.3 Surgical treatment

Patients after prostate surgery should be reviewed four to six weeks after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further re-assessment is necessary.

The following tests are recommended at follow-up visit after four to six weeks: IPSS, uroflowmetry and PVR volume.

Recommendation	LE	GR
Follow-up for all conservative, medical, or operative treatment modalities is based on empirical data or theoretical considerations, but not on evidence-based studies.	3-4	C

7. REFERENCES

- Phillips B, *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
- Abrams, P., *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*, 2002. 21: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/11857671>
- Martin, S.A., *et al.* Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. *World J Urol*, 2011. 29: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/20963421>
- Société Internationale d'Urologie (SIU), Lower Urinary Tract Symptoms (LUTS) : An International Consultation on Male LUTS. , C. Chapple & P. Abrams, Editors. 2013.
[http://www.siuurology.org/themes/web/assets/files/ICUD/pdf/Male%20Lower%20Urinary%20Tract%20Symptoms%20\(LUTS\).pdf](http://www.siuurology.org/themes/web/assets/files/ICUD/pdf/Male%20Lower%20Urinary%20Tract%20Symptoms%20(LUTS).pdf)
- Kupelian, V., *et al.* Prevalence of lower urinary tract symptoms and effect on quality of life in a racially and ethnically diverse random sample: the Boston Area Community Health (BACH) Survey. *Arch Intern Med*, 2006. 166: 2381.
<https://www.ncbi.nlm.nih.gov/pubmed/17130393>
- Agarwal, A., *et al.* What is the most bothersome lower urinary tract symptom? Individual- and population-level perspectives for both men and women. *Eur Urol*, 2014. 65: 1211.
<https://www.ncbi.nlm.nih.gov/pubmed/24486308>
- De Ridder, D., *et al.* Urgency and other lower urinary tract symptoms in men aged \geq 40 years: a Belgian epidemiological survey using the ICIQ-MLUTS questionnaire. *Int J Clin Pract*, 2015. 69: 358.
<https://www.ncbi.nlm.nih.gov/pubmed/25648652>
- Taub, D.A., *et al.* The economics of benign prostatic hyperplasia and lower urinary tract symptoms in the United States. *Curr Urol Rep*, 2006. 7: 272.
<https://www.ncbi.nlm.nih.gov/pubmed/16930498>
- Gacci, M., *et al.* Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis. *BJU Int*, 2015. 115: 24.
<https://www.ncbi.nlm.nih.gov/pubmed/24602293>
- Kogan, M.I., *et al.* Epidemiology and impact of urinary incontinence, overactive bladder, and other lower urinary tract symptoms: results of the EPIC survey in Russia, Czech Republic, and Turkey. *Curr Med Res Opin*, 2014. 30: 2119.
<https://www.ncbi.nlm.nih.gov/pubmed/24932562>
- Chapple, C.R., *et al.* Lower urinary tract symptoms revisited: a broader clinical perspective. *Eur Urol*, 2008. 54: 563.
<https://www.ncbi.nlm.nih.gov/pubmed/18423969>

12. Ficarra, V., *et al.* The role of inflammation in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and its potential impact on medical therapy. *Curr Urol Rep*, 2014. 15: 463.
<https://www.ncbi.nlm.nih.gov/pubmed/25312251>
13. He, Q., *et al.* Metabolic syndrome, inflammation and lower urinary tract symptoms: possible translational links. *Prostate Cancer Prostatic Dis*, 2016. 19: 7.
<https://www.ncbi.nlm.nih.gov/pubmed/26391088>
14. Drake, M.J. Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. *Neurourology and Urodynamics*, 2014. 33: 622.
<http://www.ncbi.nlm.nih.gov/pubmed/24838519>
15. Novara, G., *et al.* Critical Review of Guidelines for BPH Diagnosis and Treatment Strategy. *Eur Urol Suppl* 2006. 4: 418.
http://eu-acme.org/europeanurology/upload_articles/Novara2.pdf
16. McVary, K.T., *et al.* Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol*, 2011. 185: 1793.
<https://www.ncbi.nlm.nih.gov/pubmed/21420124>
17. Bosch, J., *et al.* Etiology, Patient Assessment and Predicting Outcome from Therapy. *International Consultation on Urological Diseases Male LUTS Guideline 2013*, 2013. 37
18. Martin, R.M., *et al.* Lower urinary tract symptoms and risk of prostate cancer: the HUNT 2 Cohort, Norway. *Int J Cancer*, 2008. 123: 1924.
<https://www.ncbi.nlm.nih.gov/pubmed/18661522>
19. Young, J.M., *et al.* Are men with lower urinary tract symptoms at increased risk of prostate cancer? A systematic review and critique of the available evidence. *BJU Int*, 2000. 85: 1037.
<https://www.ncbi.nlm.nih.gov/pubmed/10848691>
20. Barqawi, A.B., *et al.* Methods of developing UWIN, the modified American Urological Association symptom score. *J Urol*, 2011. 186: 940.
<https://www.ncbi.nlm.nih.gov/pubmed/21791346>
21. Barry, M.J., *et al.* The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*, 1992. 148: 1549.
<https://www.ncbi.nlm.nih.gov/pubmed/1279218>
22. Donovan, J.L., *et al.* Scoring the short form ICSmaleSF questionnaire. *International Continence Society. J Urol*, 2000. 164: 1948.
<https://www.ncbi.nlm.nih.gov/pubmed/11061889>
23. Epstein, R.S., *et al.* Validation of a new quality of life questionnaire for benign prostatic hyperplasia. *J Clin Epidemiol*, 1992. 45: 1431.
<https://www.ncbi.nlm.nih.gov/pubmed/1281223>
24. Homma, Y., *et al.* Symptom assessment tool for overactive bladder syndrome--overactive bladder symptom score. *Urology*, 2006. 68: 318.
<https://www.ncbi.nlm.nih.gov/pubmed/16904444>
25. Schou, J., *et al.* The value of a new symptom score (DAN-PSS) in diagnosing uro-dynamic infravesical obstruction in BPH. *Scand J Urol Nephrol*, 1993. 27: 489.
<https://www.ncbi.nlm.nih.gov/pubmed/7512747>
26. Homma, Y., *et al.* Core Lower Urinary Tract Symptom score (CLSS) questionnaire: a reliable tool in the overall assessment of lower urinary tract symptoms. *Int J Urol*, 2008. 15: 816.
<https://www.ncbi.nlm.nih.gov/pubmed/18657204>
27. D'Silva, K.A., *et al.* Does this man with lower urinary tract symptoms have bladder outlet obstruction?: The Rational Clinical Examination: a systematic review. *JAMA*, 2014. 312: 535.
<https://www.ncbi.nlm.nih.gov/pubmed/25096693>
28. Bryan, N.P., *et al.* Frequency volume charts in the assessment and evaluation of treatment: how should we use them? *Eur Urol*, 2004. 46: 636.
<https://www.ncbi.nlm.nih.gov/pubmed/15474275>
29. Gisolf, K.W., *et al.* Analysis and reliability of data from 24-hour frequency-volume charts in men with lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol*, 2000. 38: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/10859441>
30. Cornu, J.N., *et al.* A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. *Eur Urol*, 2012. 62: 877.
<https://www.ncbi.nlm.nih.gov/pubmed/22840350>

31. Weiss, J.P. Nocturia: "do the math". J Urol, 2006. 175: S16.
<https://www.ncbi.nlm.nih.gov/pubmed/16458734>
32. Weiss, J.P., *et al.* Nocturia Think Tank: focus on nocturnal polyuria: ICI-RS 2011. Neurourol Urodyn, 2012. 31: 330.
<https://www.ncbi.nlm.nih.gov/pubmed/22415907>
33. Vaughan, C.P., *et al.* Military exposure and urinary incontinence among American men. J Urol, 2014. 191: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/23871759>
34. Bright, E., *et al.* Urinary diaries: evidence for the development and validation of diary content, format, and duration. Neurourol Urodyn, 2011. 30: 348.
<https://www.ncbi.nlm.nih.gov/pubmed/21284023>
35. Yap, T.L., *et al.* A systematic review of the reliability of frequency-volume charts in urological research and its implications for the optimum chart duration. BJU Int, 2007. 99: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/16956355>
36. Weissfeld, J.L., *et al.* Quality control of cancer screening examination procedures in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials, 2000. 21: 390s.
<https://www.ncbi.nlm.nih.gov/pubmed/11189690>
37. Roehrborn, C.G. Accurate determination of prostate size via digital rectal examination and transrectal ultrasound. Urology, 1998. 51: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/9586952>
38. Roehrborn, C.G., *et al.* Interexaminer reliability and validity of a three-dimensional model to assess prostate volume by digital rectal examination. Urology, 2001. 57: 1087.
<https://www.ncbi.nlm.nih.gov/pubmed/11377314>
39. Bosch, J.L., *et al.* Validity of digital rectal examination and serum prostate specific antigen in the estimation of prostate volume in community-based men aged 50 to 78 years: the Krimpen Study. Eur Urol, 2004. 46: 753.
<https://www.ncbi.nlm.nih.gov/pubmed/15548443>
40. Burger, M., *et al.* ICUD-EAU International Consultation on Bladder Cancer 2012: Non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol, 2013. 63: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/22981672>
41. Bonkat, *et al.* EAU Guidelines on Urological Infections. In: EAU Guidelines, edition presented at the annual EAU Congress London 2017. ISBN 978-90-79754-91-5.
<http://uroweb.org/guidelines/>
42. Palou, J., *et al.* ICUD-EAU International Consultation on Bladder Cancer 2012: Urothelial carcinoma of the prostate. Eur Urol, 2013. 63: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/22938869>
43. Roupret, M., *et al.* European guidelines on upper tract urothelial carcinomas: 2013 update. Eur Urol, 2013. 63: 1059.
<https://www.ncbi.nlm.nih.gov/pubmed/23540953>
44. Roehrborn, C.G., *et al.* Guidelines for the diagnosis and treatment of benign prostatic hyperplasia: a comparative, international overview. Urology, 2001. 58: 642.
<https://www.ncbi.nlm.nih.gov/pubmed/11711329>
45. Abrams, P., *et al.* Evaluation and treatment of lower urinary tract symptoms in older men. J Urol, 2013. 189: S93.
<https://www.ncbi.nlm.nih.gov/pubmed/23234640>
46. European urinalysis guidelines. Scand J Clin Lab Invest Suppl, 2000. 231: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/12647764>
47. Khasriya, R., *et al.* The inadequacy of urinary dipstick and microscopy as surrogate markers of urinary tract infection in urological outpatients with lower urinary tract symptoms without acute frequency and dysuria. J Urol, 2010. 183: 1843.
<https://www.ncbi.nlm.nih.gov/pubmed/20303096>
48. Roehrborn, C.G., *et al.* Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. Urology, 1999. 53: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/10096388>
49. Bohnen, A.M., *et al.* Serum prostate-specific antigen as a predictor of prostate volume in the community: the Krimpen study. Eur Urol, 2007. 51: 1645.
<https://www.ncbi.nlm.nih.gov/pubmed/17320271>
50. Kayikci, A., *et al.* Free prostate-specific antigen is a better tool than total prostate-specific antigen at predicting prostate volume in patients with lower urinary tract symptoms. Urology, 2012. 80: 1088.
<https://www.ncbi.nlm.nih.gov/pubmed/23107399>

51. Morote, J., *et al.* Prediction of prostate volume based on total and free serum prostate-specific antigen: is it reliable? *Eur Urol*, 2000. 38: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/10859448>
52. Heidenreich, A., *et al.* EAU guidelines on prostate cancer part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol*, 2014. 65: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/24207135>
53. Roehrborn, C.G., *et al.* Serum prostate specific antigen is a strong predictor of future prostate growth in men with benign prostatic hyperplasia. PROSCAR long-term efficacy and safety study. *J Urol*, 2000. 163: 13.
<https://www.ncbi.nlm.nih.gov/pubmed/10604304>
54. Roehrborn, C.G., *et al.* Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. *Urology*, 1999. 54: 662.
<https://www.ncbi.nlm.nih.gov/pubmed/10510925>
55. Djavan, B., *et al.* Longitudinal study of men with mild symptoms of bladder outlet obstruction treated with watchful waiting for four years. *Urology*, 2004. 64: 1144.
<https://www.ncbi.nlm.nih.gov/pubmed/15596187>
56. McConnell, J.D., *et al.* The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med*, 2003. 349: 2387.
<https://www.ncbi.nlm.nih.gov/pubmed/14681504>
57. Roehrborn, C.G. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study. *BJU Int*, 2006. 97: 734.
<https://www.ncbi.nlm.nih.gov/pubmed/16536764>
58. Jacobsen, S.J., *et al.* Treatment for benign prostatic hyperplasia among community dwelling men: the Olmsted County study of urinary symptoms and health status. *J Urol*, 1999. 162: 1301.
<https://www.ncbi.nlm.nih.gov/pubmed/10492184>
59. Lim, K.B., *et al.* Comparison of intravesical prostatic protrusion, prostate volume and serum prostatic-specific antigen in the evaluation of bladder outlet obstruction. *Int J Urol*, 2006. 13: 1509.
<https://www.ncbi.nlm.nih.gov/pubmed/17118026>
60. Meigs, J.B., *et al.* Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. *J Clin Epidemiol*, 2001. 54: 935.
<https://www.ncbi.nlm.nih.gov/pubmed/11520654>
61. Gerber, G.S., *et al.* Serum creatinine measurements in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Urology*, 1997. 49: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/9145973>
62. Oelke, M., *et al.* Can we identify men who will have complications from benign prostatic obstruction (BPO)? ICI-RS 2011. *Neurourol Urodyn*, 2012. 31: 322.
<https://www.ncbi.nlm.nih.gov/pubmed/22415947>
63. Comiter, C.V., *et al.* Urodynamic risk factors for renal dysfunction in men with obstructive and nonobstructive voiding dysfunction. *J Urol*, 1997. 158: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/9186351>
64. Koch, W.F., *et al.* The outcome of renal ultrasound in the assessment of 556 consecutive patients with benign prostatic hyperplasia. *J Urol*, 1996. 155: 186.
<https://www.ncbi.nlm.nih.gov/pubmed/7490828>
65. Rule, A.D., *et al.* The association between benign prostatic hyperplasia and chronic kidney disease in community-dwelling men. *Kidney Int*, 2005. 67: 2376.
<https://www.ncbi.nlm.nih.gov/pubmed/15882282>
66. Hong, S.K., *et al.* Chronic kidney disease among men with lower urinary tract symptoms due to benign prostatic hyperplasia. *BJU Int*, 2010. 105: 1424.
<https://www.ncbi.nlm.nih.gov/pubmed/19874305>
67. Lee, J.H., *et al.* Relationship of estimated glomerular filtration rate with lower urinary tract symptoms/benign prostatic hyperplasia measures in middle-aged men with moderate to severe lower urinary tract symptoms. *Urology*, 2013. 82: 1381.
<https://www.ncbi.nlm.nih.gov/pubmed/24063940>
68. Mebust, W.K., *et al.* Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol*, 1989. 141: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/2643719>

69. Rule, A.D., *et al.* Longitudinal changes in post-void residual and voided volume among community dwelling men. *J Urol*, 2005. 174: 1317.
<https://www.ncbi.nlm.nih.gov/pubmed/16145411>
70. Sullivan, M.P., *et al.* Detrusor contractility and compliance characteristics in adult male patients with obstructive and nonobstructive voiding dysfunction. *J Urol*, 1996. 155: 1995.
<https://www.ncbi.nlm.nih.gov/pubmed/8618307>
71. Oelke, M., *et al.* Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. *Eur Urol*, 2007. 52: 827.
<https://www.ncbi.nlm.nih.gov/pubmed/17207910>
72. Mochtar, C.A., *et al.* Post-void residual urine volume is not a good predictor of the need for invasive therapy among patients with benign prostatic hyperplasia. *J Urol*, 2006. 175: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/16406914>
73. Jorgensen, J.B., *et al.* Age-related variation in urinary flow variables and flow curve patterns in elderly males. *Br J Urol*, 1992. 69: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/1373664>
74. Kranske, R., *et al.* Causes for variability in repeated pressure-flow measurements. *Urology*, 2003. 61: 930.
<https://www.ncbi.nlm.nih.gov/pubmed/12736007>
75. Reynard, J.M., *et al.* The ICS-'BPH' Study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. *Br J Urol*, 1998. 82: 619.
<https://www.ncbi.nlm.nih.gov/pubmed/9839573>
76. Idzenga, T., *et al.* Accuracy of maximum flow rate for diagnosing bladder outlet obstruction can be estimated from the ICS nomogram. *Neurourol Urodyn*, 2008. 27: 97.
<https://www.ncbi.nlm.nih.gov/pubmed/17600368>
77. Siroky, M.B., *et al.* The flow rate nomogram: I. Development. *J Urol*, 1979. 122: 665.
<https://www.ncbi.nlm.nih.gov/pubmed/159366>
78. Siroky, M.B., *et al.* The flow rate nomogram: II. Clinical correlation. *J Urol*, 1980. 123: 208.
<https://www.ncbi.nlm.nih.gov/pubmed/7354519>
79. Grossfeld, G.D., *et al.* Benign prostatic hyperplasia: clinical overview and value of diagnostic imaging. *Radiol Clin North Am*, 2000. 38: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/10664665>
80. Thorpe, A., *et al.* Benign prostatic hyperplasia. *Lancet*, 2003. 361: 1359.
<https://www.ncbi.nlm.nih.gov/pubmed/12711484>
81. Wilkinson, A.G., *et al.* Is pre-operative imaging of the urinary tract worthwhile in the assessment of prostatism? *Br J Urol*, 1992. 70: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/1379105>
82. Loch, A.C., *et al.* Technical and anatomical essentials for transrectal ultrasound of the prostate. *World J Urol*, 2007. 25: 361.
<https://www.ncbi.nlm.nih.gov/pubmed/17701043>
83. Stravodimos, K.G., *et al.* TRUS versus transabdominal ultrasound as a predictor of enucleated adenoma weight in patients with BPH: a tool for standard preoperative work-up? *Int Urol Nephrol*, 2009. 41: 767.
<https://www.ncbi.nlm.nih.gov/pubmed/19350408>
84. Shoukry, I., *et al.* Role of uroflowmetry in the assessment of lower urinary tract obstruction in adult males. *Br J Urol*, 1975. 47: 559.
<https://www.ncbi.nlm.nih.gov/pubmed/1191927>
85. Anikwe, R.M. Correlations between clinical findings and urinary flow rate in benign prostatic hypertrophy. *Int Surg*, 1976. 61: 392.
<https://www.ncbi.nlm.nih.gov/pubmed/61184>
86. el Din, K.E., *et al.* The correlation between urodynamic and cystoscopic findings in elderly men with voiding complaints. *J Urol*, 1996. 155: 1018.
<https://www.ncbi.nlm.nih.gov/pubmed/8583551>
87. Oelke, M., *et al.* Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. *Eur Urol*, 2008. 54: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/18325657>
88. Oh, M.M., *et al.* Is there a correlation between the presence of idiopathic detrusor overactivity and the degree of bladder outlet obstruction? *Urology*, 2011. 77: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/20934743>

89. Jeong, S.J., *et al.* Prevalence and Clinical Features of Detrusor Underactivity among Elderly with Lower Urinary Tract Symptoms: A Comparison between Men and Women. *Korean J Urol*, 2012. 53: 342.
<https://www.ncbi.nlm.nih.gov/pubmed/22670194>
90. Thomas, A.W., *et al.* The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *BJU Int*, 2004. 93: 745.
<https://www.ncbi.nlm.nih.gov/pubmed/15049984>
91. Al-Hayek, S., *et al.* Natural history of detrusor contractility--minimum ten-year urodynamic follow-up in men with bladder outlet obstruction and those with detrusor. *Scand J Urol Nephrol Suppl*, 2004: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/15545204>
92. Thomas, A.W., *et al.* The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic followup of transurethral resection of prostate for bladder outlet obstruction. *J Urol*, 2005. 174: 1887.
<https://www.ncbi.nlm.nih.gov/pubmed/16217330>
93. Clement, K.D., *et al.* Invasive urodynamic studies for the management of lower urinary tract symptoms (LUTS) in men with voiding dysfunction. *Cochrane Database Syst Rev*, 2015: CD011179.
<https://www.ncbi.nlm.nih.gov/pubmed/25918922>
94. Stohrer, M., *et al.* EAU guidelines on neurogenic lower urinary tract dysfunction. *Eur Urol*, 2009. 56: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/19403235>
95. Kojima, M., *et al.* Correlation of presumed circle area ratio with infravesical obstruction in men with lower urinary tract symptoms. *Urology*, 1997. 50: 548.
<https://www.ncbi.nlm.nih.gov/pubmed/9338730>
96. Chia, S.J., *et al.* Correlation of intravesical prostatic protrusion with bladder outlet obstruction. *BJU Int*, 2003. 91: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/12603417>
97. Keqin, Z., *et al.* Clinical significance of intravesical prostatic protrusion in patients with benign prostatic enlargement. *Urology*, 2007. 70: 1096.
<https://www.ncbi.nlm.nih.gov/pubmed/18158025>
98. Mariappan, P., *et al.* Intravesical prostatic protrusion is better than prostate volume in predicting the outcome of trial without catheter in white men presenting with acute urinary retention: a prospective clinical study. *J Urol*, 2007. 178: 573.
<https://www.ncbi.nlm.nih.gov/pubmed/17570437>
99. Tan, Y.H., *et al.* Intravesical prostatic protrusion predicts the outcome of a trial without catheter following acute urine retention. *J Urol*, 2003. 170: 2339.
<https://www.ncbi.nlm.nih.gov/pubmed/14634410>
100. Arnolds, M., *et al.* Positioning invasive versus noninvasive uroynamics in the assessment of bladder outlet obstruction. *Curr Opin Urol*, 2009. 19: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/19057217>
101. Manieri, C., *et al.* The diagnosis of bladder outlet obstruction in men by ultrasound measurement of bladder wall thickness. *J Urol*, 1998. 159: 761.
<https://www.ncbi.nlm.nih.gov/pubmed/9474143>
102. Kessler, T.M., *et al.* Ultrasound assessment of detrusor thickness in men--can it predict bladder outlet obstruction and replace pressure flow study? *J Urol*, 2006. 175: 2170.
<https://www.ncbi.nlm.nih.gov/pubmed/16697831>
103. Blatt, A.H., *et al.* Ultrasound measurement of bladder wall thickness in the assessment of voiding dysfunction. *J Urol*, 2008. 179: 2275.
<https://www.ncbi.nlm.nih.gov/pubmed/18423703>
104. Oelke, M. International Consultation on Incontinence-Research Society (ICI-RS) report on non-invasive uroynamics: the need of standardization of ultrasound bladder and detrusor wall thickness measurements to quantify bladder wall hypertrophy. *Neurourol Urodyn*, 2010. 29: 634.
<https://www.ncbi.nlm.nih.gov/pubmed/20432327>
105. Kojima, M., *et al.* Ultrasonic estimation of bladder weight as a measure of bladder hypertrophy in men with infravesical obstruction: a preliminary report. *Urology*, 1996. 47: 942.
<https://www.ncbi.nlm.nih.gov/pubmed/8677600>
106. Kojima, M., *et al.* Noninvasive quantitative estimation of infravesical obstruction using ultrasonic measurement of bladder weight. *J Urol*, 1997. 157: 476.
<https://www.ncbi.nlm.nih.gov/pubmed/8996337>

107. Akino, H., *et al.* Ultrasound-estimated bladder weight predicts risk of surgery for benign prostatic hyperplasia in men using alpha-adrenoceptor blocker for LUTS. *Urology*, 2008. 72: 817.
<https://www.ncbi.nlm.nih.gov/pubmed/18597835>
108. McIntosh, S.L., *et al.* Noninvasive assessment of bladder contractility in men. *J Urol*, 2004. 172: 1394.
<https://www.ncbi.nlm.nih.gov/pubmed/15371853>
109. Drinnan, M.J., *et al.* Inter-observer agreement in the estimation of bladder pressure using a penile cuff. *Neurourol Urodyn*, 2003. 22: 296.
<https://www.ncbi.nlm.nih.gov/pubmed/12808703>
110. Griffiths, C.J., *et al.* A nomogram to classify men with lower urinary tract symptoms using urine flow and noninvasive measurement of bladder pressure. *J Urol*, 2005. 174: 1323.
<https://www.ncbi.nlm.nih.gov/pubmed/16145412>
111. Clarkson, B., *et al.* Continuous non-invasive measurement of bladder voiding pressure using an experimental constant low-flow test. *Neurourol Urodyn*, 2012. 31: 557.
<https://www.ncbi.nlm.nih.gov/pubmed/22190105>
112. Van Mastrigt, R., *et al.* Towards a noninvasive urodynamic diagnosis of infravesical obstruction. *BJU Int*, 1999. 84: 195.
<https://www.ncbi.nlm.nih.gov/pubmed/10444152>
113. Pel, J.J., *et al.* Development of a non-invasive strategy to classify bladder outlet obstruction in male patients with LUTS. *Neurourol Urodyn*, 2002. 21: 117.
<https://www.ncbi.nlm.nih.gov/pubmed/11857664>
114. Shinbo, H., *et al.* Application of ultrasonography and the resistive index for evaluating bladder outlet obstruction in patients with benign prostatic hyperplasia. *Curr Urol Rep*, 2011. 12: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/21475953>
115. Ku, J.H., *et al.* Correlation between prostatic urethral angle and bladder outlet obstruction index in patients with lower urinary tract symptoms. *Urology*, 2010. 75: 1467.
<https://www.ncbi.nlm.nih.gov/pubmed/19962734>
116. Malde, S., *et al.* Systematic Review of the Performance of Noninvasive Tests in Diagnosing Bladder Outlet Obstruction in Men with Lower Urinary Tract Symptoms. *Eur Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27687821>
117. Ball, A.J., *et al.* The natural history of untreated "prostatism". *Br J Urol*, 1981. 53: 613.
<https://www.ncbi.nlm.nih.gov/pubmed/6172172>
118. Kirby, R.S. The natural history of benign prostatic hyperplasia: what have we learned in the last decade? *Urology*, 2000. 56: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/11074195>
119. Isaacs, J.T. Importance of the natural history of benign prostatic hyperplasia in the evaluation of pharmacologic intervention. *Prostate Suppl*, 1990. 3: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/1689166>
120. Netto, N.R., Jr., *et al.* Evaluation of patients with bladder outlet obstruction and mild international prostate symptom score followed up by watchful waiting. *Urology*, 1999. 53: 314.
<https://www.ncbi.nlm.nih.gov/pubmed/9933046>
121. Flanigan, R.C., *et al.* 5-year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. *J Urol*, 1998. 160: 12.
<https://www.ncbi.nlm.nih.gov/pubmed/9628595>
122. Wasson, J.H., *et al.* A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. *N Engl J Med*, 1995. 332: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/7527493>
123. Brown, C.T., *et al.* Self management for men with lower urinary tract symptoms: randomised controlled trial. *Bmj*, 2007. 334: 25.
<https://www.ncbi.nlm.nih.gov/pubmed/17118949>
124. Yap, T.L., *et al.* The impact of self-management of lower urinary tract symptoms on frequency-volume chart measures. *BJU Int*, 2009. 104: 1104.
<https://www.ncbi.nlm.nih.gov/pubmed/19485993>
125. Brown, C.T., *et al.* Defining the components of a self-management programme for men with uncomplicated lower urinary tract symptoms: a consensus approach. *Eur Urol*, 2004. 46: 254.
<https://www.ncbi.nlm.nih.gov/pubmed/15245822>

126. Michel, M.C., *et al.* Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. *Br J Pharmacol*, 2006. 147 Suppl 2: S88.
<https://www.ncbi.nlm.nih.gov/pubmed/16465187>
127. Kortmann, B.B., *et al.* Urodynamic effects of alpha-adrenoceptor blockers: a review of clinical trials. *Urology*, 2003. 62: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/12837408>
128. Barendrecht, M.M., *et al.* Do alpha1-adrenoceptor antagonists improve lower urinary tract symptoms by reducing bladder outlet resistance? *Neurourol Urodyn*, 2008. 27: 226.
<https://www.ncbi.nlm.nih.gov/pubmed/17638312>
129. Djavan, B., *et al.* State of the art on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Urology*, 2004. 64: 1081.
<https://www.ncbi.nlm.nih.gov/pubmed/15596173>
130. Michel, M.C., *et al.* Comparison of tamsulosin efficacy in subgroups of patients with lower urinary tract symptoms. *Prostate Cancer Prostatic Dis*, 1998. 1: 332.
<https://www.ncbi.nlm.nih.gov/pubmed/12496876>
131. Boyle, P., *et al.* Meta-analysis of randomized trials of terazosin in the treatment of benign prostatic hyperplasia. *Urology*, 2001. 58: 717.
<https://www.ncbi.nlm.nih.gov/pubmed/11711348>
132. Roehrborn, C.G. Three months' treatment with the alpha1-blocker alfuzosin does not affect total or transition zone volume of the prostate. *Prostate Cancer Prostatic Dis*, 2006. 9: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/16304557>
133. Roehrborn, C.G., *et al.* The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol*, 2008. 179: 616.
<https://www.ncbi.nlm.nih.gov/pubmed/18082216>
134. Roehrborn, C.G., *et al.* The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol*, 2010. 57: 123.
<https://www.ncbi.nlm.nih.gov/pubmed/19825505>
135. Nickel, J.C., *et al.* A meta-analysis of the vascular-related safety profile and efficacy of alpha-adrenergic blockers for symptoms related to benign prostatic hyperplasia. *Int J Clin Pract*, 2008. 62: 1547.
<https://www.ncbi.nlm.nih.gov/pubmed/18822025>
136. Barendrecht, M.M., *et al.* Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: the cardiovascular system. *BJU Int*, 2005. 95 Suppl 4: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/15871732>
137. Chapple, C.R., *et al.* Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. *Eur Urol*, 2011. 59: 342.
<https://www.ncbi.nlm.nih.gov/pubmed/21109344>
138. Welk, B., *et al.* The risk of fall and fracture with the initiation of a prostate-selective alpha antagonist: a population based cohort study. *BMJ*, 2015. 351: h5398.
<https://www.ncbi.nlm.nih.gov/pubmed/26502947>
139. Chang, D.F., *et al.* Intraoperative floppy iris syndrome associated with tamsulosin. *J Cataract Refract Surg*, 2005. 31: 664.
<https://www.ncbi.nlm.nih.gov/pubmed/15899440>
140. Chatziralli, I.P., *et al.* Risk factors for intraoperative floppy iris syndrome: a meta-analysis. *Ophthalmology*, 2011. 118: 730.
<https://www.ncbi.nlm.nih.gov/pubmed/21168223>
141. van Dijk, M.M., *et al.* Effects of alpha(1)-adrenoceptor antagonists on male sexual function. *Drugs*, 2006. 66: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/16526818>
142. Gacci, M., *et al.* Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. *J Sex Med*, 2014. 11: 1554.
<https://www.ncbi.nlm.nih.gov/pubmed/24708055>
143. Andriole, G., *et al.* Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. *J Urol*, 2004. 172: 1399.
<https://www.ncbi.nlm.nih.gov/pubmed/15371854>

144. Rittmaster, R.S., *et al.* Evidence for atrophy and apoptosis in the prostates of men given finasteride. *J Clin Endocrinol Metab*, 1996. 81: 814.
<https://www.ncbi.nlm.nih.gov/pubmed/8636309>
145. Naslund, M.J., *et al.* A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. *Clin Ther*, 2007. 29: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/17379044>
146. Andersen, J.T., *et al.* Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo-controlled study. The Scandinavian BPH Study Group. *Urology*, 1995. 46: 631.
<https://www.ncbi.nlm.nih.gov/pubmed/7495111>
147. Kirby, R.S., *et al.* Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology*, 2003. 61: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/12559281>
148. Lepor, H., *et al.* The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *N Engl J Med*, 1996. 335: 533.
<https://www.ncbi.nlm.nih.gov/pubmed/8684407>
149. Marberger, M.J. Long-term effects of finasteride in patients with benign prostatic hyperplasia: a double-blind, placebo-controlled, multicenter study. PROWESS Study Group. *Urology*, 1998. 51: 677.
<https://www.ncbi.nlm.nih.gov/pubmed/9610579>
150. McConnell, J.D., *et al.* The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med*, 1998. 338: 557.
<https://www.ncbi.nlm.nih.gov/pubmed/9475762>
151. Nickel, J.C., *et al.* Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian Two year Study. *Cmaj*, 1996. 155: 1251.
<https://www.ncbi.nlm.nih.gov/pubmed/8911291>
152. Roehrborn, C.G., *et al.* Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology*, 2002. 60: 434.
<https://www.ncbi.nlm.nih.gov/pubmed/12350480>
153. Nickel, J.C., *et al.* Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). *BJU Int*, 2011. 108: 388.
<https://www.ncbi.nlm.nih.gov/pubmed/21631695>
154. Boyle, P., *et al.* Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology*, 1996. 48: 398.
<https://www.ncbi.nlm.nih.gov/pubmed/8804493>
155. Gittelman, M., *et al.* Dutasteride improves objective and subjective disease measures in men with benign prostatic hyperplasia and modest or severe prostate enlargement. *J Urol*, 2006. 176: 1045.
<https://www.ncbi.nlm.nih.gov/pubmed/16890688>
156. Roehrborn, C.G., *et al.* Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5alpha-reductase inhibitor dutasteride: results of 4-year studies. *BJU Int*, 2005. 96: 572.
<https://www.ncbi.nlm.nih.gov/pubmed/16104912>
157. Roehrborn, C.G., *et al.* The influence of baseline parameters on changes in international prostate symptom score with dutasteride, tamsulosin, and combination therapy among men with symptomatic benign prostatic hyperplasia and an enlarged prostate: 2-year data from the CombAT study. *Eur Urol*, 2009. 55: 461.
<https://www.ncbi.nlm.nih.gov/pubmed/19013011>
158. Roehrborn, C.G. BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. *BJU Int*, 2008. 101 Suppl 3: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/18307681>
159. Andersen, J.T., *et al.* Finasteride significantly reduces acute urinary retention and need for surgery in patients with symptomatic benign prostatic hyperplasia. *Urology*, 1997. 49: 839.
<https://www.ncbi.nlm.nih.gov/pubmed/9187688>
160. Kirby, R.S., *et al.* Long-term urodynamic effects of finasteride in benign prostatic hyperplasia: a pilot study. *Eur Urol*, 1993. 24: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/7689971>

161. Tammela, T.L., *et al.* Long-term effects of finasteride on invasive urodynamics and symptoms in the treatment of patients with bladder outflow obstruction due to benign prostatic hyperplasia. *J Urol*, 1995. 154: 1466.
<https://www.ncbi.nlm.nih.gov/pubmed/7544845>
162. Donohue, J.F., *et al.* Transurethral prostate resection and bleeding: a randomized, placebo controlled trial of role of finasteride for decreasing operative blood loss. *J Urol*, 2002. 168: 2024.
<https://www.ncbi.nlm.nih.gov/pubmed/12394700>
163. Andriole, G.L., *et al.* Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*, 2010. 362: 1192.
<https://www.ncbi.nlm.nih.gov/pubmed/20357281>
164. Thompson, I.M., *et al.* The influence of finasteride on the development of prostate cancer. *N Engl J Med*, 2003. 349: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/12824459>
165. Hsieh, T.F., *et al.* Use of 5-alpha-reductase inhibitors did not increase the risk of cardiovascular diseases in patients with benign prostate hyperplasia: a five-year follow-up study. *PLoS One*, 2015. 10: e0119694.
<https://www.ncbi.nlm.nih.gov/pubmed/25803433>
166. Chess-Williams, R., *et al.* The minor population of M3-receptors mediate contraction of human detrusor muscle in vitro. *J Auton Pharmacol*, 2001. 21: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/12123469>
167. Matsui, M., *et al.* Multiple functional defects in peripheral autonomic organs in mice lacking muscarinic acetylcholine receptor gene for the M3 subtype. *Proc Natl Acad Sci U S A*, 2000. 97: 9579.
<https://www.ncbi.nlm.nih.gov/pubmed/10944224>
168. Kono, M., *et al.* Central muscarinic receptor subtypes regulating voiding in rats. *J Urol*, 2006. 175: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/16406941>
169. Wuest, M., *et al.* Effect of rilimakalim on detrusor contraction in the presence and absence of urothelium. *Naunyn Schmiedebergs Arch Pharmacol*, 2005. 372: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/16283254>
170. Goldfischer, E.R., *et al.* Efficacy and safety of oxybutynin topical gel 3% in patients with urgency and/or mixed urinary incontinence: A randomized, double-blind, placebo-controlled study. *Neurourology and Urodynamics*, 2015. 34: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/24133005>
171. Baldwin, C.M., *et al.* Transdermal oxybutynin. *Drugs*, 2009. 69: 327.
<https://www.ncbi.nlm.nih.gov/pubmed/19275276>
172. Chapple, C.R., *et al.* A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. *Eur Urol*, 2006. 49: 651.
<https://www.ncbi.nlm.nih.gov/pubmed/16530611>
173. Michel, M.C., *et al.* Does gender or age affect the efficacy and safety of tolterodine? *J Urol*, 2002. 168: 1027.
<https://www.ncbi.nlm.nih.gov/pubmed/12187215>
174. Chapple, C., *et al.* Fesoterodine clinical efficacy and safety for the treatment of overactive bladder in relation to patient profiles: a systematic review. *Curr Med Res Opin*, 2015. 31: 1201.
<https://www.ncbi.nlm.nih.gov/pubmed/25798911>
175. Dmochowski, R., *et al.* Efficacy and tolerability of tolterodine extended release in male and female patients with overactive bladder. *Eur Urol*, 2007. 51: 1054.
<https://www.ncbi.nlm.nih.gov/pubmed/17097217>
176. Herschorn, S., *et al.* Efficacy and tolerability of fesoterodine in men with overactive bladder: a pooled analysis of 2 phase III studies. *Urology*, 2010. 75: 1149.
<https://www.ncbi.nlm.nih.gov/pubmed/19914702>
177. Hofner, K., *et al.* Safety and efficacy of tolterodine extended release in men with overactive bladder symptoms and presumed non-obstructive benign prostatic hyperplasia. *World J Urol*, 2007. 25: 627.
<https://www.ncbi.nlm.nih.gov/pubmed/17906864>
178. Roehrborn, C.G., *et al.* Efficacy and tolerability of tolterodine extended-release in men with overactive bladder and urgency urinary incontinence. *BJU Int*, 2006. 97: 1003.
<https://www.ncbi.nlm.nih.gov/pubmed/16643482>

179. Kaplan, S.A., *et al.* Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *Jama*, 2006. 296: 2319.
<https://www.ncbi.nlm.nih.gov/pubmed/17105794>
180. Kaplan, S.A., *et al.* Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol*, 2005. 174: 2273.
<https://www.ncbi.nlm.nih.gov/pubmed/16280803>
181. Kaplan, S.A., *et al.* Solifenacin treatment in men with overactive bladder: effects on symptoms and patient-reported outcomes. *Aging Male*, 2010. 13: 100.
<https://www.ncbi.nlm.nih.gov/pubmed/20001469>
182. Roehrborn, C.G., *et al.* Effects of serum PSA on efficacy of tolterodine extended release with or without tamsulosin in men with LUTS, including OAB. *Urology*, 2008. 72: 1061.
<https://www.ncbi.nlm.nih.gov/pubmed/18817961>
183. Yokoyama, T., *et al.* Naftopidil and propiverine hydrochloride for treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant overactive bladder: a prospective randomized controlled study. *Scand J Urol Nephrol*, 2009. 43: 307.
<https://www.ncbi.nlm.nih.gov/pubmed/19396723>
184. Abrams, P., *et al.* Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol*, 2006. 175: 999.
<https://www.ncbi.nlm.nih.gov/pubmed/16469601>
185. Giuliano, F., *et al.* The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. *Eur Urol*, 2013. 63: 506.
<https://www.ncbi.nlm.nih.gov/pubmed/23018163>
186. Morelli, A., *et al.* Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats. *J Sex Med*, 2011. 8: 2746.
<https://www.ncbi.nlm.nih.gov/pubmed/21812935>
187. Vignozzi, L., *et al.* PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE5 inhibitors in LUTS. *Prostate*, 2013. 73: 1391.
<https://www.ncbi.nlm.nih.gov/pubmed/23765639>
188. Gacci, M., *et al.* A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol*, 2012. 61: 994.
<https://www.ncbi.nlm.nih.gov/pubmed/22405510>
189. Oelke, M., *et al.* Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. *Eur Urol*, 2012. 61: 917.
<https://www.ncbi.nlm.nih.gov/pubmed/22297243>
190. Oelke, M., *et al.* Time to onset of clinically meaningful improvement with tadalafil 5 mg once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: analysis of data pooled from 4 pivotal, double-blind, placebo controlled studies. *J Urol*, 2015. 193: 1581.
<https://www.ncbi.nlm.nih.gov/pubmed/25437533>
191. Donatucci, C.F., *et al.* Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. *BJU Int*, 2011. 107: 1110.
<https://www.ncbi.nlm.nih.gov/pubmed/21244606>
192. Porst, H., *et al.* Efficacy and safety of tadalafil 5 mg once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: subgroup analyses of pooled data from 4 multinational, randomized, placebo-controlled clinical studies. *Urology*, 2013. 82: 667.
<https://www.ncbi.nlm.nih.gov/pubmed/23876588>
193. Vlachopoulos, C., *et al.* Impact of cardiovascular risk factors and related comorbid conditions and medical therapy reported at baseline on the treatment response to tadalafil 5 mg once-daily in men with lower urinary tract symptoms associated with benign prostatic hyperplasia: an integrated analysis of four randomised, double-blind, placebo-controlled, clinical trials. *Int J Clin Pract*, 2015. 69: 1496.
<https://www.ncbi.nlm.nih.gov/pubmed/26299520>
194. Porst, H., *et al.* Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia and on erectile dysfunction in sexually active men with both conditions: analyses of pooled data from four randomized, placebo-controlled tadalafil clinical studies. *J Sex Med*, 2013. 10: 2044.
<https://www.ncbi.nlm.nih.gov/pubmed/23782459>

195. Brock, G.B., *et al.* Direct effects of tadalafil on lower urinary tract symptoms versus indirect effects mediated through erectile dysfunction symptom improvement: integrated data analyses from 4 placebo controlled clinical studies. *J Urol*, 2014. 191: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/24096120>
196. Roehrborn, C.G., *et al.* Effects of tadalafil once daily on maximum urinary flow rate in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *J Urol*, 2014. 191: 1045.
<https://www.ncbi.nlm.nih.gov/pubmed/24445278>
197. Casabe, A., *et al.* Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. *J Urol*, 2014. 191: 727.
<https://www.ncbi.nlm.nih.gov/pubmed/24096118>
198. Gacci, M., *et al.* The use of a single daily dose of tadalafil to treat signs and symptoms of benign prostatic hyperplasia and erectile dysfunction. *Res Rep Urol*, 2013. 5: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/24400241>
199. Madersbacher, S., *et al.* Plant extracts: sense or nonsense? *Curr Opin Urol*, 2008. 18: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/18090484>
200. Buck, A.C. Is there a scientific basis for the therapeutic effects of serenoa repens in benign prostatic hyperplasia? Mechanisms of action. *J Urol*, 2004. 172: 1792.
<https://www.ncbi.nlm.nih.gov/pubmed/15540722>
201. Levin, R.M., *et al.* A scientific basis for the therapeutic effects of Pygeum africanum and Serenoa repens. *Urol Res*, 2000. 28: 201.
<https://www.ncbi.nlm.nih.gov/pubmed/10929430>
202. Habib, F.K., *et al.* Not all brands are created equal: a comparison of selected components of different brands of Serenoa repens extract. *Prostate Cancer Prostatic Dis*, 2004. 7: 195.
<https://www.ncbi.nlm.nih.gov/pubmed/15289814>
203. Scaglione, F., *et al.* Comparison of the potency of different brands of Serenoa repens extract on 5alpha-reductase types I and II in prostatic co-cultured epithelial and fibroblast cells. *Pharmacology*, 2008. 82: 270.
<https://www.ncbi.nlm.nih.gov/pubmed/18849646>
204. De Monte, C., *et al.* Modern extraction techniques and their impact on the pharmacological profile of Serenoa repens extracts for the treatment of lower urinary tract symptoms. *BMC Urol*, 2014. 14: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/25112532>
205. Tacklind, J., *et al.* Serenoa repens for benign prostatic hyperplasia. *Cochrane Database Syst Rev*, 2012. 12: Cd001423.
<https://www.ncbi.nlm.nih.gov/pubmed/23235581>
206. Wilt, T., *et al.* Pygeum africanum for benign prostatic hyperplasia. *Cochrane Database Syst Rev*, 2002: Cd001044.
<https://www.ncbi.nlm.nih.gov/pubmed/11869585>
207. Wilt, T., *et al.* Cernilton for benign prostatic hyperplasia. *Cochrane Database Syst Rev*, 2000: Cd001042.
<https://www.ncbi.nlm.nih.gov/pubmed/10796739>
208. Morgia, G., *et al.* Serenoa repens, lycopene and selenium versus tamsulosin for the treatment of LUTS/BPH. An Italian multicenter double-blinded randomized study between single or combination therapy (PROCOMB trial). *Prostate*, 2014. 74: 1471.
<https://www.ncbi.nlm.nih.gov/pubmed/25154739>
209. Ryu, Y.W., *et al.* Comparison of tamsulosin plus serenoa repens with tamsulosin in the treatment of benign prostatic hyperplasia in Korean men: 1-year randomized open label study. *Urol Int*, 2015. 94: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/25614155>
210. Chapple, C.R., *et al.* Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. *Eur Urol*, 2013. 63: 296.
<https://www.ncbi.nlm.nih.gov/pubmed/23195283>
211. Herschorn, S., *et al.* A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the beta(3) adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. *Urology*, 2013. 82: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/23769122>

212. Khullar, V., *et al.* Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. *Eur Urol*, 2013. 63: 283.
<https://www.ncbi.nlm.nih.gov/pubmed/23182126>
213. Nitti, V.W., *et al.* Results of a randomized phase III trial of mirabegron in patients with overactive bladder. *J Urol*, 2013. 189: 1388.
<https://www.ncbi.nlm.nih.gov/pubmed/23079373>
214. Yamaguchi, O., *et al.* Efficacy and Safety of the Selective beta3 -Adrenoceptor Agonist Mirabegron in Japanese Patients with Overactive Bladder: A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study. *Low Urin Tract Symptoms*, 2015. 7: 84.
<https://www.ncbi.nlm.nih.gov/pubmed/26663687>
215. Drake, M.J., *et al.* Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE). *Eur Urol*, 2016. 70: 136.
<https://www.ncbi.nlm.nih.gov/pubmed/26965560>
216. Kuo, H.C., *et al.* Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a beta3-adrenoceptor agonist, in patients with overactive bladder in Asia. *Neurourol Urodyn*, 2015. 34: 685.
<https://www.ncbi.nlm.nih.gov/pubmed/25130281>
217. Nitti, V.W., *et al.* Urodynamics and safety of the beta(3)-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. *J Urol*, 2013. 190: 1320.
<https://www.ncbi.nlm.nih.gov/pubmed/23727415>
218. Van Gelderen, M., *et al.* Absence of clinically relevant cardiovascular interaction upon add-on of mirabegron or tamsulosin to an established tamsulosin or mirabegron treatment in healthy middle-aged to elderly men. *International Journal of Clinical Pharmacology and Therapeutics*, 2014. 52: 693.
<https://www.ncbi.nlm.nih.gov/pubmed/24755125>
219. Ichihara, K., *et al.* A randomized controlled study of the efficacy of tamsulosin monotherapy and its combination with mirabegron for overactive bladder induced by benign prostatic obstruction. *Journal of Urology*, 2015. 193: 921.
<https://www.ncbi.nlm.nih.gov/pubmed/25254938>
220. Yamaguchi, O., *et al.* Safety and efficacy of mirabegron as 'add-on' therapy in patients with overactive bladder treated with solifenacin: a post-marketing, open-label study in Japan (MILAI study). *BJU Int*, 2015. 116: 612.
<https://www.ncbi.nlm.nih.gov/pubmed/25639296>
221. Debruyne, F.M., *et al.* Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. European ALFIN Study Group. *Eur Urol*, 1998. 34: 169.
<https://www.ncbi.nlm.nih.gov/pubmed/9732187>
222. Barkin, J., *et al.* Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. *Eur Urol*, 2003. 44: 461.
<https://www.ncbi.nlm.nih.gov/pubmed/14499682>
223. Nickel, J.C., *et al.* Finasteride monotherapy maintains stable lower urinary tract symptoms in men with benign prostatic hyperplasia following cessation of alpha blockers. *Can Urol Assoc J*, 2008. 2: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/18542722>
224. Athanasopoulos, A., *et al.* Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. *J Urol*, 2003. 169: 2253.
<https://www.ncbi.nlm.nih.gov/pubmed/12771763>
225. Roehrborn, C.G., *et al.* Efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin treatment (Duodart®) compared with watchful waiting with initiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naive men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results. *BJU Int*, 2015. 116: 450.
<https://www.ncbi.nlm.nih.gov/pubmed/25565364>
226. Roehrborn, C.G., *et al.* Influence of baseline variables on changes in International Prostate Symptom Score after combined therapy with dutasteride plus tamsulosin or either monotherapy in patients with benign prostatic hyperplasia and lower urinary tract symptoms: 4-year results of the CombAT study. *BJU Int*, 2014. 113: 623.
<https://www.ncbi.nlm.nih.gov/pubmed/24127818>

227. Chapple, C., *et al.* Tolterodine treatment improves storage symptoms suggestive of overactive bladder in men treated with alpha-blockers. *Eur Urol*, 2009. 56: 534.
<https://www.ncbi.nlm.nih.gov/pubmed/19070418>
228. Kaplan, S.A., *et al.* Safety and tolerability of solifenacin add-on therapy to alpha-blocker treated men with residual urgency and frequency. *J Urol*, 2009. 182: 2825.
<https://www.ncbi.nlm.nih.gov/pubmed/19837435>
229. Lee, J.Y., *et al.* Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. *BJU Int*, 2004. 94: 817.
<https://www.ncbi.nlm.nih.gov/pubmed/15476515>
230. Lee, K.S., *et al.* Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: a prospective, randomized, controlled multicenter study. *J Urol*, 2005. 174: 1334.
<https://www.ncbi.nlm.nih.gov/pubmed/16155414>
231. MacDiarmid, S.A., *et al.* Efficacy and safety of extended-release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double-blind, placebo-controlled study. *Mayo Clin Proc*, 2008. 83: 1002.
<https://www.ncbi.nlm.nih.gov/pubmed/18775200>
232. Saito, H., *et al.* A comparative study of the efficacy and safety of tamsulosin hydrochloride (Harnal capsules) alone and in combination with propiverine hydrochloride (BUP-4 tablets) in patients with prostatic hypertrophy associated with pollakisuria and/or urinary incontinence. *Jpn J Urol Surg*, 1999. 12: 525. (No abstract available).
233. Yang, Y., *et al.* Efficacy and safety of combined therapy with terazosin and tolteradine for patients with lower urinary tract symptoms associated with benign prostatic hyperplasia: a prospective study. *Chin Med J (Engl)*, 2007. 120: 370.
<https://www.ncbi.nlm.nih.gov/pubmed/17376305>
234. Maruyama, O., *et al.* Naftopidil monotherapy vs naftopidil and an anticholinergic agent combined therapy for storage symptoms associated with benign prostatic hyperplasia: A prospective randomized controlled study. *Int J Urol*, 2006. 13: 1280.
<https://www.ncbi.nlm.nih.gov/pubmed/17010005>
235. Lee, H.N., *et al.* Rate and associated factors of solifenacin add-on after tamsulosin monotherapy in men with voiding and storage lower urinary tract symptoms. *International Journal of Clinical Practice*, 2015. 69: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/25363606>
236. van Kerrebroeck, P., *et al.* Combination therapy with solifenacin and tamsulosin oral controlled absorption system in a single tablet for lower urinary tract symptoms in men: efficacy and safety results from the randomised controlled NEPTUNE trial. *Eur Urol*, 2013. 64: 1003.
<https://www.ncbi.nlm.nih.gov/pubmed/23932438>
237. Kaplan, S.A., *et al.* Add-on fesoterodine for residual storage symptoms suggestive of overactive bladder in men receiving alpha-blocker treatment for lower urinary tract symptoms. *BJU Int*, 2012. 109: 1831.
<https://www.ncbi.nlm.nih.gov/pubmed/21966995>
238. Kim, T.H., *et al.* Comparison of the efficacy and safety of tolterodine 2 mg and 4 mg combined with an alpha-blocker in men with lower urinary tract symptoms (LUTS) and overactive bladder: a randomized controlled trial. *BJU Int*, 2016. 117: 307.
<https://www.ncbi.nlm.nih.gov/pubmed/26305143>
239. Athanasopoulos, A., *et al.* The role of antimuscarinics in the management of men with symptoms of overactive bladder associated with concomitant bladder outlet obstruction: an update. *Eur Urol*, 2011. 60: 94.
<https://www.ncbi.nlm.nih.gov/pubmed/21497434>
240. Kaplan, S.A., *et al.* Antimuscarinics for treatment of storage lower urinary tract symptoms in men: a systematic review. *Int J Clin Pract*, 2011. 65: 487.
<https://www.ncbi.nlm.nih.gov/pubmed/21210910>
241. Van Kerrebroeck, P., *et al.* Efficacy and safety of solifenacin plus tamsulosin OCAS in men with voiding and storage lower urinary tract symptoms: results from a phase 2, dose-finding study (SATURN). *Eur Urol*, 2013. 64: 398.
<https://www.ncbi.nlm.nih.gov/pubmed/23537687>

242. Drake, M.J., *et al.* Long-term safety and efficacy of single-tablet combinations of solifenacin and tamsulosin oral controlled absorption system in men with storage and voiding lower urinary tract symptoms: Results from the NEPTUNE study and NEPTUNE II open-label extension. *European Urology*, 2015. 67: 262.
<https://www.ncbi.nlm.nih.gov/pubmed/25070148>
243. Drake, M.J., *et al.* Responder and health-related quality of life analyses in men with lower urinary tract symptoms treated with a fixed-dose combination of solifenacin and tamsulosin OCAS: results from the NEPTUNE study. *BJU Int*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25907003>
244. Gong, M., *et al.* Tamsulosin combined with solifenacin versus tamsulosin monotherapy for male lower urinary tract symptoms: a meta-analysis. *Curr Med Res Opin*, 2015. 31: 1781.
<https://www.ncbi.nlm.nih.gov/pubmed/26211817>
245. Kaplan, S.A., *et al.* Solifenacin plus tamsulosin combination treatment in men with lower urinary tract symptoms and bladder outlet obstruction: a randomized controlled trial. *Eur Urol*, 2013. 63: 158.
<https://www.ncbi.nlm.nih.gov/pubmed/22831853>
246. Ahyai, S.A., *et al.* Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement. *Eur Urol*, 2010. 58: 384.
<https://www.ncbi.nlm.nih.gov/pubmed/20825758>
247. Reich, O., *et al.* Techniques and long-term results of surgical procedures for BPH. *Eur Urol*, 2006. 49: 970.
<https://www.ncbi.nlm.nih.gov/pubmed/16481092>
248. Dorflinger, T., *et al.* Transurethral prostatectomy compared with incision of the prostate in the treatment of prostatism caused by small benign prostate glands. *Scand J Urol Nephrol*, 1992. 26: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/1284003>
249. Jahanson, S., *et al.* Transurethral incision versus resection of the prostate for small to medium benign prostatic hyperplasia. *Br J Urol*, 1998. 81: 276.
<https://www.ncbi.nlm.nih.gov/pubmed/9488072>
250. Lourenco, T., *et al.* The clinical effectiveness of transurethral incision of the prostate: a systematic review of randomised controlled trials. *World J Urol*, 2010. 28: 23.
<https://www.ncbi.nlm.nih.gov/pubmed/20033744>
251. Riehmman, M., *et al.* Transurethral resection versus incision of the prostate: a randomized, prospective study. *Urology*, 1995. 45: 768.
<https://www.ncbi.nlm.nih.gov/pubmed/7538238>
252. Saporta, L., *et al.* Objective and subjective comparison of transurethral resection, transurethral incision and balloon dilatation of the prostate. A prospective study. *Eur Urol*, 1996. 29: 439.
<https://www.ncbi.nlm.nih.gov/pubmed/8791051>
253. Soonawalla, P.F., *et al.* Transurethral incision versus transurethral resection of the prostate. A subjective and objective analysis. *Br J Urol*, 1992. 70: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/1382793>
254. Tkocz, M., *et al.* Comparison of long-term results of transurethral incision of the prostate with transurethral resection of the prostate, in patients with benign prostatic hypertrophy. *Neurourol Urodyn*, 2002. 21: 112.
<https://www.ncbi.nlm.nih.gov/pubmed/11857663>
255. Yang, Q., *et al.* Transurethral incision compared with transurethral resection of the prostate for bladder outlet obstruction: a systematic review and meta-analysis of randomized controlled trials. *J Urol*, 2001. 165: 1526.
<https://www.ncbi.nlm.nih.gov/pubmed/11342911>
256. Madersbacher, S., *et al.* Is transurethral resection of the prostate still justified? *BJU Int*, 1999. 83: 227.
<https://www.ncbi.nlm.nih.gov/pubmed/10233485>
257. Madersbacher, S., *et al.* Reoperation, myocardial infarction and mortality after transurethral and open prostatectomy: a nation-wide, long-term analysis of 23,123 cases. *Eur Urol*, 2005. 47: 499.
<https://www.ncbi.nlm.nih.gov/pubmed/15774249>
258. Reich, O., *et al.* Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. *J Urol*, 2008. 180: 246.
<https://www.ncbi.nlm.nih.gov/pubmed/18499179>

259. Roos, N.P., *et al.* Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. *N Engl J Med*, 1989. 320: 1120.
<https://www.ncbi.nlm.nih.gov/pubmed/2469015>
260. Hahn, R.G., *et al.* Incidence of acute myocardial infarction and cause-specific mortality after transurethral treatments of prostatic hypertrophy. *Urology*, 2000. 55: 236.
<https://www.ncbi.nlm.nih.gov/pubmed/10688086>
261. Holman, C.D., *et al.* Mortality and prostate cancer risk in 19,598 men after surgery for benign prostatic hyperplasia. *BJU Int*, 1999. 84: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/10444122>
262. Shalev, M., *et al.* Long-term incidence of acute myocardial infarction after open and transurethral resection of the prostate for benign prostatic hyperplasia. *J Urol*, 1999. 161: 491.
<https://www.ncbi.nlm.nih.gov/pubmed/9915433>
263. Rassweiler, J., *et al.* Complications of transurethral resection of the prostate (TURP)--incidence, management, and prevention. *Eur Urol*, 2006. 50: 969.
<https://www.ncbi.nlm.nih.gov/pubmed/16469429>
264. Issa, M.M. Technological advances in transurethral resection of the prostate: bipolar versus monopolar TURP. *J Endourol*, 2008. 22: 1587.
<https://www.ncbi.nlm.nih.gov/pubmed/18721041>
265. Rassweiler, J., *et al.* Bipolar transurethral resection of the prostate--technical modifications and early clinical experience. *Minim Invasive Ther Allied Technol*, 2007. 16: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/17365673>
266. Mamoulakis, C., *et al.* Bipolar versus monopolar transurethral resection of the prostate for lower urinary tract symptoms secondary to benign prostatic obstruction. *Cochrane Database Syst Rev*, 2014. 1.
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009629.pub3/abstract>
267. Burke, N., *et al.* Systematic review and meta-analysis of transurethral resection of the prostate versus minimally invasive procedures for the treatment of benign prostatic obstruction. *Urology*, 2010. 75: 1015.
<https://www.ncbi.nlm.nih.gov/pubmed/19854492>
268. Mamoulakis, C., *et al.* Bipolar versus monopolar transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. *Eur Urol*, 2009. 56: 798.
<https://www.ncbi.nlm.nih.gov/pubmed/19595501>
269. Omar, M.I., *et al.* Systematic review and meta-analysis of the clinical effectiveness of bipolar compared with monopolar transurethral resection of the prostate (TURP). *BJU Int*, 2014. 113: 24.
<https://www.ncbi.nlm.nih.gov/pubmed/24053602>
270. Cornu, J.N., *et al.* A Systematic Review and Meta-analysis of Functional Outcomes and Complications Following Transurethral Procedures for Lower Urinary Tract Symptoms Resulting from Benign Prostatic Obstruction: An Update. *Eur Urol*, 2015. 67: 1066.
<https://www.ncbi.nlm.nih.gov/pubmed/24972732>
271. Autorino, R., *et al.* Four-year outcome of a prospective randomised trial comparing bipolar plasmakinetic and monopolar transurethral resection of the prostate. *Eur Urol*, 2009. 55: 922.
<https://www.ncbi.nlm.nih.gov/pubmed/19185975>
272. Chen, Q., *et al.* Bipolar transurethral resection in saline vs traditional monopolar resection of the prostate: results of a randomized trial with a 2-year follow-up. *BJU Int*, 2010. 106: 1339.
<https://www.ncbi.nlm.nih.gov/pubmed/20477825>
273. Fagerstrom, T., *et al.* Complications and clinical outcome 18 months after bipolar and monopolar transurethral resection of the prostate. *J Endourol*, 2011. 25: 1043.
<https://www.ncbi.nlm.nih.gov/pubmed/21568691>
274. Geavlete, B., *et al.* Bipolar plasma vaporization vs monopolar and bipolar TURP-A prospective, randomized, long-term comparison. *Urology*, 2011. 78: 930.
<https://www.ncbi.nlm.nih.gov/pubmed/2180212>
275. Giulianelli, R., *et al.* Comparative randomized study on the efficaciousness of endoscopic bipolar prostate resection versus monopolar resection technique. 3 year follow-up. *Arch Ital Urol Androl*, 2013. 85: 86.
<https://www.ncbi.nlm.nih.gov/pubmed/23820656>
276. Mamoulakis, C., *et al.* Midterm results from an international multicentre randomised controlled trial comparing bipolar with monopolar transurethral resection of the prostate. *Eur Urol*, 2013. 63: 667.
<https://www.ncbi.nlm.nih.gov/pubmed/23102675>

277. Xie, C.Y., *et al.* Five-year follow-up results of a randomized controlled trial comparing bipolar plasmakinetic and monopolar transurethral resection of the prostate. *Yonsei Med J*, 2012. 53: 734. <https://www.ncbi.nlm.nih.gov/pubmed/22665339>
278. Komura, K., *et al.* Incidence of urethral stricture after bipolar transurethral resection of the prostate using TURis: results from a randomised trial. *BJU Int*, 2015. 115: 644. <https://www.ncbi.nlm.nih.gov/pubmed/24909399>
279. Stucki, P., *et al.* Bipolar versus monopolar transurethral resection of the prostate: a prospective randomized trial focusing on bleeding complications. *J Urol*, 2015. 193: 1371. <https://www.ncbi.nlm.nih.gov/pubmed/25464004>
280. Akman, T., *et al.* : a prospective randomized comparative study. *BJU Int*, 2013. 111: 129. Effects of bipolar and monopolar transurethral resection of the prostate on urinary and erectile function <https://www.ncbi.nlm.nih.gov/pubmed/22672229>
281. Mamoulakis, C., *et al.* Bipolar vs monopolar transurethral resection of the prostate: evaluation of the impact on overall sexual function in an international randomized controlled trial setting. *BJU Int*, 2013. 112: 109. <https://www.ncbi.nlm.nih.gov/pubmed/23490008>
282. Kuntz, R.M., *et al.* Holmium laser enucleation of the prostate versus open prostatectomy for prostates greater than 100 grams: 5-year follow-up results of a randomised clinical trial. *Eur Urol*, 2008. 53: 160. <https://www.ncbi.nlm.nih.gov/pubmed/17869409>
283. Naspro, R., *et al.* Holmium laser enucleation of the prostate versus open prostatectomy for prostates >70 g: 24-month follow-up. *Eur Urol*, 2006. 50: 563. <https://www.ncbi.nlm.nih.gov/pubmed/16713070>
284. Skolarikos, A., *et al.* Eighteen-month results of a randomized prospective study comparing transurethral photoselective vaporization with transvesical open enucleation for prostatic adenomas greater than 80 cc. *J Endourol*, 2008. 22: 2333. <https://www.ncbi.nlm.nih.gov/pubmed/18837655>
285. Ou, R., *et al.* Transurethral enucleation and resection of the prostate vs transvesical prostatectomy for prostate volumes >80 mL: a prospective randomized study. *BJU Int*, 2013. 112: 239. <https://www.ncbi.nlm.nih.gov/pubmed/23795788>
286. Rao, J.M., *et al.* Plasmakinetic enucleation of the prostate versus transvesical open prostatectomy for benign prostatic hyperplasia >80 mL: 12-month follow-up results of a randomized clinical trial. *Urology*, 2013. 82: 176. <https://www.ncbi.nlm.nih.gov/pubmed/23601443>
287. Zhang, Y., *et al.* [Transurethral holmium laser enucleation for prostate adenoma greater than 100 g]. *Zhonghua Nan Ke Xue*, 2007. 13: 1091. <https://www.ncbi.nlm.nih.gov/pubmed/18284057>
288. Geavlete, B., *et al.* Bipolar plasma enucleation of the prostate vs open prostatectomy in large benign prostatic hyperplasia cases - a medium term, prospective, randomized comparison. *BJU Int*, 2013. 111: 793. <https://www.ncbi.nlm.nih.gov/pubmed/23469933>
289. Geavlete, B., *et al.* Bipolar vaporization, resection, and enucleation versus open prostatectomy: optimal treatment alternatives in large prostate cases? *J Endourol*, 2015. 29: 323. <https://www.ncbi.nlm.nih.gov/pubmed/25111385>
290. Varkarakis, I., *et al.* Long-term results of open transvesical prostatectomy from a contemporary series of patients. *Urology*, 2004. 64: 306. <https://www.ncbi.nlm.nih.gov/pubmed/15302484>
291. Gratzke, C., *et al.* Complications and early postoperative outcome after open prostatectomy in patients with benign prostatic enlargement: results of a prospective multicenter study. *J Urol*, 2007. 177: 1419. <https://www.ncbi.nlm.nih.gov/pubmed/17382744>
292. Chen, S., *et al.* Plasmakinetic enucleation of the prostate compared with open prostatectomy for prostates larger than 100 grams: a randomized noninferiority controlled trial with long-term results at 6 years. *Eur Urol*, 2014. 66: 284. <https://www.ncbi.nlm.nih.gov/pubmed/24502959>
293. Li, M., *et al.* Endoscopic enucleation versus open prostatectomy for treating large benign prostatic hyperplasia: a meta-analysis of randomized controlled trials. *PLoS One*, 2015. 10: e0121265. <https://www.ncbi.nlm.nih.gov/pubmed/25826453>

294. Lin, Y., *et al.* Transurethral enucleation of the prostate versus transvesical open prostatectomy for large benign prostatic hyperplasia: a systematic review and meta-analysis of randomized controlled trials. *World J Urol*, 2016. 34: 1207.
<https://www.ncbi.nlm.nih.gov/pubmed/26699627>
295. Tubaro, A., *et al.* A prospective study of the safety and efficacy of suprapubic transvesical prostatectomy in patients with benign prostatic hyperplasia. *J Urol*, 2001. 166: 172.
<https://www.ncbi.nlm.nih.gov/pubmed/11435849>
296. Hoffman, R.M., *et al.* Microwave thermotherapy for benign prostatic hyperplasia. *Cochrane Database Syst Rev*, 2012. 9: Cd004135.
<https://www.ncbi.nlm.nih.gov/pubmed/22972068>
297. Gravas, S., *et al.* Seeking evidence that cell kill guided thermotherapy gives results not inferior to those of transurethral prostate resection: results of a pooled analysis of 3 studies of feedback transurethral microwave thermotherapy. *J Urol*, 2005. 174: 1002.
<https://www.ncbi.nlm.nih.gov/pubmed/16094023>
298. Aagaard, M.F., *et al.* Transurethral microwave thermotherapy treatment of chronic urinary retention in patients unsuitable for surgery. *Scand J Urol*, 2014. 48: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/24102183>
299. Kellner, D.S., *et al.* Efficacy of high-energy transurethral microwave thermotherapy in alleviating medically refractory urinary retention due to benign prostatic hyperplasia. *Urology*, 2004. 64: 703.
<https://www.ncbi.nlm.nih.gov/pubmed/15491705>
300. Naqvi, S.A., *et al.* High-energy microwave thermotherapy in patients in urinary retention. *J Endourol*, 2000. 14: 677.
<https://www.ncbi.nlm.nih.gov/pubmed/11083411>
301. Schelin, S. Microwave thermotherapy in patients with benign prostatic hyperplasia and chronic urinary retention. *Eur Urol*, 2001. 39: 400.
<https://www.ncbi.nlm.nih.gov/pubmed/11306877>
302. Gravas, S., *et al.* Durability of 30-minute high-energy transurethral microwave therapy for treatment of benign prostatic hyperplasia: a study of 213 patients with and without urinary retention. *Urology*, 2007. 69: 854.
<https://www.ncbi.nlm.nih.gov/pubmed/17482921>
303. de la Rosette, J.J., *et al.* Transurethral microwave thermotherapy: the gold standard for minimally invasive therapies for patients with benign prostatic hyperplasia? *J Endourol*, 2003. 17: 245.
<https://www.ncbi.nlm.nih.gov/pubmed/12816589>
304. D'Ancona, F.C., *et al.* Results of high-energy transurethral microwave thermotherapy in patients categorized according to the American Society of Anesthesiologists operative risk classification. *Urology*, 1999. 53: 322.
<https://www.ncbi.nlm.nih.gov/pubmed/9933048>
305. Boyle, P., *et al.* A meta-analysis of trials of transurethral needle ablation for treating symptomatic benign prostatic hyperplasia. *BJU Int*, 2004. 94: 83.
<https://www.ncbi.nlm.nih.gov/pubmed/15217437>
306. Bouza, C., *et al.* Systematic review and meta-analysis of Transurethral Needle Ablation in symptomatic Benign Prostatic Hyperplasia. *BMC Urol*, 2006. 6: 14.
<https://www.ncbi.nlm.nih.gov/pubmed/16790044>
307. Campo, B., *et al.* Transurethral needle ablation (TUNA) of the prostate: a clinical and urodynamic evaluation. *Urology*, 1997. 49: 847.
<https://www.ncbi.nlm.nih.gov/pubmed/9187689>
308. Steele, G.S., *et al.* Transurethral needle ablation of the prostate: a urodynamic based study with 2-year followup. *J Urol*, 1997. 158: 1834.
<https://www.ncbi.nlm.nih.gov/pubmed/9334612>
309. Chapple, C.R., *et al.* Transurethral needle ablation (TUNA). A critical review of radiofrequency thermal therapy in the management of benign prostatic hyperplasia. *Eur Urol*, 1999. 35: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/9933805>
310. Schatzl, G., *et al.* The early postoperative morbidity of transurethral resection of the prostate and of 4 minimally invasive treatment alternatives. *J Urol*, 1997. 158: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/9186334>
311. Gilling, P.J., *et al.* Combination holmium and Nd:YAG laser ablation of the prostate: initial clinical experience. *J Endourol*, 1995. 9: 151.
<https://www.ncbi.nlm.nih.gov/pubmed/7633476>

312. Toher, R., *et al.* A systematic review of holmium laser prostatectomy for benign prostatic hyperplasia. *J Urol*, 2004. 171: 1773.
<https://www.ncbi.nlm.nih.gov/pubmed/15076275>
313. Westenberg, A., *et al.* Holmium laser resection of the prostate versus transurethral resection of the prostate: results of a randomized trial with 4-year minimum long-term followup. *J Urol*, 2004. 172: 616.
<https://www.ncbi.nlm.nih.gov/pubmed/15247745>
314. Lourenco, T., *et al.* Alternative approaches to endoscopic ablation for benign enlargement of the prostate: systematic review of randomised controlled trials. *Bmj*, 2008. 337: a449.
<https://www.ncbi.nlm.nih.gov/pubmed/18595932>
315. Tan, A., *et al.* Meta-analysis of holmium laser enucleation versus transurethral resection of the prostate for symptomatic prostatic obstruction. *Br J Surg*, 2007. 94: 1201.
<https://www.ncbi.nlm.nih.gov/pubmed/17729384>
316. Yin, L., *et al.* Holmium laser enucleation of the prostate versus transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. *J Endourol*, 2013. 27: 604.
<https://www.ncbi.nlm.nih.gov/pubmed/23167266>
317. Elmansy, H., *et al.* Holmium laser enucleation versus photoselective vaporization for prostatic adenoma greater than 60 ml: preliminary results of a prospective, randomized clinical trial. *J Urol*, 2012. 188: 216.
<https://www.ncbi.nlm.nih.gov/pubmed/22591968>
318. Elshal, A.M., *et al.* Two laser ablation techniques for a prostate less than 60 mL: lessons learned 70 months after a randomized controlled trial. *Urology*, 2013. 82: 416.
<https://www.ncbi.nlm.nih.gov/pubmed/23791215>
319. Gilling, P.J., *et al.* Long-term results of a randomized trial comparing holmium laser enucleation of the prostate and transurethral resection of the prostate: results at 7 years. *BJU Int*, 2012. 109: 408.
<https://www.ncbi.nlm.nih.gov/pubmed/21883820>
320. Elmansy, H.M., *et al.* Holmium laser enucleation of the prostate: long-term durability of clinical outcomes and complication rates during 10 years of followup. *J Urol*, 2011. 186: 1972.
<https://www.ncbi.nlm.nih.gov/pubmed/21944127>
321. Gilling, P.J., *et al.* Holmium: YAG laser resection of the prostate (HoLRP) versus transurethral electrocautery resection of the prostate (TURP): a prospective randomized, urodynamicbased clinical trial. *J Urol*, 1997. 157: 149A. [No abstract available]
322. Elzayat, E.A., *et al.* Holmium laser enucleation of the prostate (HoLEP): long-term results, reoperation rate, and possible impact of the learning curve. *Eur Urol*, 2007. 52: 1465.
<https://www.ncbi.nlm.nih.gov/pubmed/17498867>
323. Tyson, M.D., *et al.* Safety of holmium laser enucleation of the prostate in anticoagulated patients. *J Endourol*, 2009. 23: 1343.
<https://www.ncbi.nlm.nih.gov/pubmed/>
324. Elzayat, E., *et al.* Holmium laser enucleation of the prostate in patients on anticoagulant therapy or with bleeding disorders. *J Urol*, 2006. 175: 1428.
<https://www.ncbi.nlm.nih.gov/pubmed/16516015>
325. Elzayat, E.A., *et al.* Holmium laser enucleation of prostate for patients in urinary retention. *Urology*, 2005. 66: 789.
<https://www.ncbi.nlm.nih.gov/pubmed/16230139>
326. Peterson, M.D., *et al.* Holmium laser enucleation of the prostate for men with urinary retention. *J Urol*, 2005. 174: 998.
<https://www.ncbi.nlm.nih.gov/pubmed/16094022>
327. Briganti, A., *et al.* Impact on sexual function of holmium laser enucleation versus transurethral resection of the prostate: results of a prospective, 2-center, randomized trial. *J Urol*, 2006. 175: 1817.
<https://www.ncbi.nlm.nih.gov/pubmed/16600770>
328. Du, C., *et al.* Holmium laser enucleation of the prostate: the safety, efficacy, and learning experience in China. *J Endourol*, 2008. 22: 1031.
<https://www.ncbi.nlm.nih.gov/pubmed/18377236>
329. Thangasamy, I.A., *et al.* Photoselective vaporisation of the prostate using 80-W and 120-W laser versus transurethral resection of the prostate for benign prostatic hyperplasia: a systematic review with meta-analysis from 2002 to 2012. *Eur Urol*, 2012. 62: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/22575913>

330. Bouchier-Hayes, D.M., *et al.* A randomized trial of photoselective vaporization of the prostate using the 80-W potassium-titanyl-phosphate laser vs transurethral prostatectomy, with a 1-year follow-up. *BJU Int*, 2010. 105: 964.
<https://www.ncbi.nlm.nih.gov/pubmed/19912196>
331. Capitan, C., *et al.* GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: a randomized clinical trial with 2-year follow-up. *Eur Urol*, 2011. 60: 734.
<https://www.ncbi.nlm.nih.gov/pubmed/21658839>
332. Skolarikos, A., *et al.*, 80W PVP versus TURP: results of a randomized prospective study at 12 months of follow-up. , in Abstract presented at: American Urological Association annual meeting. 2008: Orlando, FL, USA.
333. Hai, M.A. Photoselective vaporization of prostate: five-year outcomes of entire clinic patient population. *Urology*, 2009. 73: 807.
<https://www.ncbi.nlm.nih.gov/pubmed/19200589>
334. Ruszat, R., *et al.* GreenLight laser vaporization of the prostate: single-center experience and long-term results after 500 procedures. *Eur Urol*, 2008. 54: 893.
<https://www.ncbi.nlm.nih.gov/pubmed/18486311>
335. Hamann, M.F., *et al.* Functional outcome following photoselective vaporisation of the prostate (PVP): urodynamic findings within 12 months follow-up. *Eur Urol*, 2008. 54: 902.
<https://www.ncbi.nlm.nih.gov/pubmed/18502565>
336. Al-Ansari, A., *et al.* GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for treatment of benign prostatic hyperplasia: a randomized clinical trial with midterm follow-up. *Eur Urol*, 2010. 58: 349.
<https://www.ncbi.nlm.nih.gov/pubmed/20605316>
337. Pereira-Correia, J.A., *et al.* GreenLight HPS 120-W laser vaporization vs transurethral resection of the prostate (<60 mL): a 2-year randomized double-blind prospective urodynamic investigation. *BJU Int*, 2012. 110: 1184.
<https://www.ncbi.nlm.nih.gov/pubmed/22257240>
338. Bachmann, A., *et al.* 180-W XPS GreenLight laser therapy for benign prostate hyperplasia: early safety, efficacy, and perioperative outcome after 201 procedures. *Eur Urol*, 2012. 61: 600.
<https://www.ncbi.nlm.nih.gov/pubmed/22153927>
339. Chung, D.E., *et al.* Outcomes and complications after 532 nm laser prostatectomy in anticoagulated patients with benign prostatic hyperplasia. *J Urol*, 2011. 186: 977.
<https://www4.ncbi.nlm.nih.gov/pubmed/21791350>
340. Reich, O., *et al.* High power (80 W) potassium-titanyl-phosphate laser vaporization of the prostate in 66 high risk patients. *J Urol*, 2005. 173: 158.
<https://www.ncbi.nlm.nih.gov/pubmed/15592063>
341. Ruszat, R., *et al.* Safety and effectiveness of photoselective vaporization of the prostate (PVP) in patients on ongoing oral anticoagulation. *Eur Urol*, 2007. 51: 1031.
<https://www.ncbi.nlm.nih.gov/pubmed/16945475>
342. Sandhu, J.S., *et al.* Photoselective laser vaporization prostatectomy in men receiving anticoagulants. *J Endourol*, 2005. 19: 1196.
<https://www.ncbi.nlm.nih.gov/pubmed/16359214>
343. Woo, H., *et al.* Outcome of GreenLight HPS 120-W laser therapy in specific patient populations: those in retention, on anticoagulants, and with large prostates (>80 ml). *Eur Urol Suppl* 2008. 7: 378.
[http://www.europeanurology.com/article/S1569-9056\(08\)00027-4/abstract/outcome-of-greenlight-hps-120-w-laser-therapy-in-specific-patient-populations-those-in-retention-on-anticoagulants-and-with-large-prostates-x02265-80ml](http://www.europeanurology.com/article/S1569-9056(08)00027-4/abstract/outcome-of-greenlight-hps-120-w-laser-therapy-in-specific-patient-populations-those-in-retention-on-anticoagulants-and-with-large-prostates-x02265-80ml)
344. Rajbabu, K., *et al.* Photoselective vaporization of the prostate with the potassium-titanyl-phosphate laser in men with prostates of >100 mL. *BJU Int*, 2007. 100: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/17511771>
345. Ruszat, R., *et al.* Photoselective vaporization of the prostate: subgroup analysis of men with refractory urinary retention. *Eur Urol*, 2006. 50: 1040.
<https://www.ncbi.nlm.nih.gov/pubmed/16481099>
346. Horasanli, K., *et al.* Photoselective potassium titanyl phosphate (KTP) laser vaporization versus transurethral resection of the prostate for prostates larger than 70 mL: a short-term prospective randomized trial. *Urology*, 2008. 71: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/18308094>

347. Alivizatos, G., *et al.* Transurethral photoselective vaporization versus transvesical open enucleation for prostatic adenomas >80ml: 12-mo results of a randomized prospective study. *Eur Urol*, 2008. 54: 427.
<https://www.ncbi.nlm.nih.gov/pubmed/18069117>
348. Bouchier-Hayes, D.M., *et al.* KTP laser versus transurethral resection: early results of a randomized trial. *J Endourol*, 2006. 20: 580.
<https://www.ncbi.nlm.nih.gov/pubmed/16903819>
349. Bruyere, F., *et al.* Influence of photoselective vaporization of the prostate on sexual function: results of a prospective analysis of 149 patients with long-term follow-up. *Eur Urol*, 2010. 58: 207.
<https://www.ncbi.nlm.nih.gov/pubmed/20466480>
350. Thomas, J.A., *et al.* A Multicenter Randomized Noninferiority Trial Comparing GreenLight-XPS Laser Vaporization of the Prostate and Transurethral Resection of the Prostate for the Treatment of Benign Prostatic Obstruction: Two-yr Outcomes of the GOLIATH Study. *Eur Urol*, 2016. 69: 94.
<https://www.ncbi.nlm.nih.gov/pubmed/26283011>
351. Bach, T., *et al.* Laser treatment of benign prostatic obstruction: basics and physical differences. *Eur Urol*, 2012. 61: 317.
<https://www.ncbi.nlm.nih.gov/pubmed/22033173>
352. Chiang, P.H., *et al.* GreenLight HPS laser 120-W versus diode laser 200-W vaporization of the prostate: comparative clinical experience. *Lasers Surg Med*, 2010. 42: 624.
<https://www.ncbi.nlm.nih.gov/pubmed/20806388>
353. Ruszat, R., *et al.* Prospective single-centre comparison of 120-W diode-pumped solid-state high-intensity system laser vaporization of the prostate and 200-W high-intensive diode-laser ablation of the prostate for treating benign prostatic hyperplasia. *BJU Int*, 2009. 104: 820.
<https://www.ncbi.nlm.nih.gov/pubmed/19239441>
354. Seitz, M., *et al.* The diode laser: a novel side-firing approach for laser vaporisation of the human prostate--immediate efficacy and 1-year follow-up. *Eur Urol*, 2007. 52: 1717.
<https://www.ncbi.nlm.nih.gov/pubmed/17628326>
355. Shaker, H.S., *et al.* Quartz head contact laser fiber: a novel fiber for laser ablation of the prostate using the 980 nm high power diode laser. *J Urol*, 2012. 187: 575.
<https://www.ncbi.nlm.nih.gov/pubmed/22177175>
356. Erol, A., *et al.* High power diode laser vaporization of the prostate: preliminary results for benign prostatic hyperplasia. *J Urol*, 2009. 182: 1078.
<https://www.ncbi.nlm.nih.gov/pubmed/19616811>
357. Hruby, S., *et al.* Eraser laser enucleation of the prostate: technique and results. *Eur Urol*, 2013. 63: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/22959050>
358. Leonardi, R. Preliminary results on selective light vaporization with the side-firing 980 nm diode laser in benign prostatic hyperplasia: an ejaculation sparing technique. *Prostate Cancer Prostatic Dis*, 2009. 12: 277.
<https://www.ncbi.nlm.nih.gov/pubmed/19322136>
359. Xu, A., *et al.* A randomized trial comparing diode laser enucleation of the prostate with plasmakinetic enucleation and resection of the prostate for the treatment of benign prostatic hyperplasia. *J Endourol*, 2013. 27: 1254.
<https://www.ncbi.nlm.nih.gov/pubmed/23879477>
360. Lusuardi, L., *et al.* Safety and efficacy of Eraser laser enucleation of the prostate: preliminary report. *J Urol*, 2011. 186: 1967.
<https://www.ncbi.nlm.nih.gov/pubmed/21944122>
361. Razzaghi, M.R., *et al.* Diode laser (980 nm) vaporization in comparison with transurethral resection of the prostate for benign prostatic hyperplasia: randomized clinical trial with 2-year follow-up. *Urology*, 2014. 84: 526.
<https://www.ncbi.nlm.nih.gov/pubmed/25168526>
362. Tiburtius, C., *et al.* A prospective, randomized comparison of a 1940 nm and a 2013 nm thulium: yttrium-aluminum-garnet laser device for Thulium VapoEnucleation of the prostate (ThuVEP): First results. *Indian J Urol*, 2015. 31: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/25624576>
363. Cui, D., *et al.* A randomized trial comparing thulium laser resection to standard transurethral resection of the prostate for symptomatic benign prostatic hyperplasia: four-year follow-up results. *World J Urol*, 2014. 32: 683.
<https://www.ncbi.nlm.nih.gov/pubmed/23913094>

364. Fu, W.J., *et al.* Comparison of 2-microm continuous wave laser vaporesction of the prostate and transurethral resection of the prostate: a prospective nonrandomized trial with 1-year follow-up. *Urology*, 2010. 75: 194.
<https://www.ncbi.nlm.nih.gov/pubmed/19819535>
365. Xia, S.J., *et al.* Thulium laser versus standard transurethral resection of the prostate: a randomized prospective trial. *Eur Urol*, 2008. 53: 382.
<https://www.ncbi.nlm.nih.gov/pubmed/17566639>
366. Peng, B., *et al.* A comparative study of thulium laser resection of the prostate and bipolar transurethral plasmakinetic prostatectomy for treating benign prostatic hyperplasia. *BJU Int*, 2013. 111: 633.
<https://www.ncbi.nlm.nih.gov/pubmed/23107074>
367. Yang, Z., *et al.* Thulium laser enucleation versus plasmakinetic resection of the prostate: a randomized prospective trial with 18-month follow-up. *Urology*, 2013. 81: 396.
<https://www.ncbi.nlm.nih.gov/pubmed/23374815>
368. Bach, T., *et al.* Thulium:YAG vapoenucleation in large volume prostates. *J Urol*, 2011. 186: 2323.
<https://www.ncbi.nlm.nih.gov/pubmed/22014812>
369. Hauser, S., *et al.* Thulium laser (Revolix) vapoenucleation of the prostate is a safe procedure in patients with an increased risk of hemorrhage. *Urol Int*, 2012. 88: 390.
<https://www.ncbi.nlm.nih.gov/pubmed/22627127>
370. Netsch, C., *et al.* Comparison of 120-200 W 2 mum thulium:yttrium-aluminum-garnet vapoenucleation of the prostate. *J Endourol*, 2012. 26: 224.
<https://www.ncbi.nlm.nih.gov/pubmed/22191688>
371. Netsch, C., *et al.* 120-W 2-microm thulium:yttrium-aluminium-garnet vapoenucleation of the prostate: 12-month follow-up. *BJU Int*, 2012. 110: 96.
<https://www.ncbi.nlm.nih.gov/pubmed/22085294>
372. Feng, L., *et al.* Thulium Laser Enucleation Versus Plasmakinetic Enucleation of the Prostate: A Randomized Trial of a Single Center. *J Endourol*, 2016. 30: 665.
<https://www.ncbi.nlm.nih.gov/pubmed/26886719>
373. Netsch, C., *et al.* Safety and effectiveness of Thulium VapoEnucleation of the prostate (ThuVEP) in patients on anticoagulant therapy. *World J Urol*, 2014. 32: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/23657354>
374. Szlauer, R., *et al.* Endoscopic vaporesction of the prostate using the continuous-wave 2-microm thulium laser: outcome and demonstration of the surgical technique. *Eur Urol*, 2009. 55: 368.
<https://www.ncbi.nlm.nih.gov/pubmed/19022557>
375. Bach, T., *et al.* Thulium:YAG laser enucleation (VapoEnucleation) of the prostate: safety and durability during intermediate-term follow-up. *World J Urol*, 2010. 28: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/19669645>
376. Zhang, F., *et al.* Thulium laser versus holmium laser transurethral enucleation of the prostate: 18-month follow-up data of a single center. *Urology*, 2012. 79: 869.
<https://www.ncbi.nlm.nih.gov/pubmed/22342411>
377. Gross, A.J., *et al.* Complications and early postoperative outcome in 1080 patients after thulium vapoenucleation of the prostate: results at a single institution. *Eur Urol*, 2013. 63: 859.
<https://www.ncbi.nlm.nih.gov/pubmed/23245687>
378. Tiburtius, C., *et al.* Impact of thulium VapoEnucleation of the prostate on erectile function: a prospective analysis of 72 patients at 12-month follow-up. *Urology*, 2014. 83: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/> <https://www.ncbi.nlm.nih.gov/pubmed/24103563>
379. Wang, Y., *et al.* Impact of 120-W 2-mum continuous wave laser vapoenucleation of the prostate on sexual function. *Lasers Med Sci*, 2014. 29: 689.
<https://www.ncbi.nlm.nih.gov/pubmed/23828495>
380. Sun, F., *et al.* Long-term results of thulium laser resection of the prostate: a prospective study at multiple centers. *World J Urol*, 2015. 33: 503.
<https://www.ncbi.nlm.nih.gov/pubmed/25487702>
381. Chang, C.H., *et al.* Vapoenucleation of the prostate using a high-power thulium laser: a one-year follow-up study. *BMC Urol*, 2015. 15: 40.
<https://www.ncbi.nlm.nih.gov/pubmed/25956819>
382. Corica, A.P., *et al.* A novel temporary prostatic stent for the relief of prostatic urethral obstruction. *BJU Int*, 2004. 93: 346.
<https://www.ncbi.nlm.nih.gov/pubmed/14764134>

383. Guazzoni, G., *et al.* A modified prostatic UroLume Wallstent for healthy patients with symptomatic benign prostatic hyperplasia: a European Multicenter Study. *Urology*, 1994. 44: 364.
<https://www.ncbi.nlm.nih.gov/pubmed/7521092>
384. Vanderbrink, B.A., *et al.* Prostatic stents for the treatment of benign prostatic hyperplasia. *Curr Opin Urol*, 2007. 17: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/17143103>
385. Gesenberg, A., *et al.* Management of benign prostatic hyperplasia in high risk patients: long-term experience with the Memotherm stent. *J Urol*, 1998. 160: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/9628608>
386. Kaplan, S.A., *et al.* Long-term experience utilizing a new balloon expandable prostatic endoprosthesis: the Titan stent. North American Titan Stent Study Group. *Urology*, 1995. 45: 234.
<https://www.ncbi.nlm.nih.gov/pubmed/7855972>
387. Perry, M.J., *et al.* Thermo-expandable intraprostatic stents in bladder outlet obstruction: an 8-year study. *BJU Int*, 2002. 90: 216.
<https://www.ncbi.nlm.nih.gov/pubmed/12133055>
388. van Dijk, M.M., *et al.* The bell-shaped nitinol prostatic stent in the treatment of lower urinary tract symptoms: experience in 108 patients. *Eur Urol*, 2006. 49: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/16426738>
389. Kijvikai, K., *et al.* Clinical utility of "blind placement" prostatic stent in patients with benign prostatic obstruction: a prospective study. *Urology*, 2006. 68: 1025.
<https://www.ncbi.nlm.nih.gov/pubmed/17113894>
390. Armitage, J.N., *et al.* Epithelializing stent for benign prostatic hyperplasia: a systematic review of the literature. *J Urol*, 2007. 177: 1619.
<https://www.ncbi.nlm.nih.gov/pubmed/17437773>
391. Masood, S., *et al.* The 12-year outcome analysis of an endourethral wallstent for treating benign prostatic hyperplasia. *BJU Int*, 2004. 94: 1271.
<https://www.ncbi.nlm.nih.gov/pubmed/15610103>
392. Armitage, J.N., *et al.* The thermo-expandable metallic stent for managing benign prostatic hyperplasia: a systematic review. *BJU Int*, 2006. 98: 806.
<https://www.ncbi.nlm.nih.gov/pubmed/16879446>
393. Chin, P.T., *et al.* Prostatic urethral lift: two-year results after treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Urology*, 2012. 79: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/22202539>
394. McNicholas, T.A., *et al.* Minimally invasive prostatic urethral lift: surgical technique and multinational experience. *Eur Urol*, 2013. 64: 292.
<https://www.ncbi.nlm.nih.gov/pubmed/23357348>
395. Roehrborn, C.G., *et al.* The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. Study. *J Urol*, 2013. 190: 2161.
<https://www.ncbi.nlm.nih.gov/pubmed/23764081>
396. Woo, H.H., *et al.* Safety and feasibility of the prostatic urethral lift: a novel, minimally invasive treatment for lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). *BJU Int*, 2011. 108: 82.
<https://www.ncbi.nlm.nih.gov/pubmed/21554526>
397. Woo, H.H., *et al.* Preservation of sexual function with the prostatic urethral lift: a novel treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Sex Med*, 2012. 9: 568.
<https://www.ncbi.nlm.nih.gov/pubmed/22172161>
398. Perera, M., *et al.* Prostatic urethral lift improves urinary symptoms and flow while preserving sexual function for men with benign prostatic hyperplasia: a systematic review and meta-analysis. *Eur Urol*, 2015. 67: 704.
<https://www.ncbi.nlm.nih.gov/pubmed/25466940>
399. Sonksen, J., *et al.* Prospective, Randomized, Multinational Study of Prostatic Urethral Lift Versus Transurethral Resection of the Prostate: 12-month Results from the BPH6 Study. *Eur Urol*, 2015. 68: 643.
<https://www.ncbi.nlm.nih.gov/pubmed/25937539>
400. Roehrborn, C.G., *et al.* Three year results of the prostatic urethral L.I.F.T. study. *Can J Urol*, 2015. 22: 7772.
<https://www.ncbi.nlm.nih.gov/pubmed/25937539>

401. Magistro, G., *et al.* New intraprostatic injectables and prostatic urethral lift for male LUTS. *Nat Rev Urol*, 2015. 12: 461.
<https://www.ncbi.nlm.nih.gov/pubmed/26195444>
402. Marberger, M., *et al.* A randomized double-blind placebo-controlled phase 2 dose-ranging study of onabotulinumtoxinA in men with benign prostatic hyperplasia. *Eur Urol*, 2013. 63: 496.
<https://www.ncbi.nlm.nih.gov/pubmed/9610579>
403. McVary, K.T., *et al.* A multicenter, randomized, double-blind, placebo controlled study of onabotulinumtoxinA 200 U to treat lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol*, 2014. 192: 150.
<https://www.ncbi.nlm.nih.gov/pubmed/24508634>
404. Shim, S.R., *et al.* Efficacy and safety of botulinum toxin injection for benign prostatic hyperplasia: a systematic review and meta-analysis. *Int Urol Nephrol*, 2016. 48: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/26560471>
405. Elhilali, M.M., *et al.* Prospective, randomized, double-blind, vehicle controlled, multicenter phase IIb clinical trial of the pore forming protein PRX302 for targeted treatment of symptomatic benign prostatic hyperplasia. *J Urol*, 2013. 189: 1421.
<https://www.ncbi.nlm.nih.gov/pubmed/23142202>
406. Denmeade, S.R., *et al.* Phase 1 and 2 studies demonstrate the safety and efficacy of intraprostatic injection of PRX302 for the targeted treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol*, 2011. 59: 747.
<https://www.ncbi.nlm.nih.gov/pubmed/21129846>
407. Mariano, M.B., *et al.* Laparoscopic prostatectomy with vascular control for benign prostatic hyperplasia. *J Urol*, 2002. 167: 2528.
<https://www.ncbi.nlm.nih.gov/pubmed/11992078>
408. Sotelo, R., *et al.* Robotic simple prostatectomy. *J Urol*, 2008. 179: 513.
<https://www.ncbi.nlm.nih.gov/pubmed/18076926>
409. Autorino, R., *et al.* Perioperative Outcomes of Robotic and Laparoscopic Simple Prostatectomy: A European-American Multi-institutional Analysis. *Eur Urol*, 2015. 68: 86.
<https://www.ncbi.nlm.nih.gov/pubmed/25484140>
410. Pokorny, M., *et al.* Robot-assisted Simple Prostatectomy for Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Enlargement: Surgical Technique and Outcomes in a High-volume Robotic Centre. *Eur Urol*, 2015. 68: 451.
<https://www.ncbi.nlm.nih.gov/pubmed/25887786>
411. Martin Garzon, O.D., *et al.* One-Year Outcome Comparison of Laparoscopic, Robotic, and Robotic Intrafascial Simple Prostatectomy for Benign Prostatic Hyperplasia. *J Endourol*, 2016. 30: 312.
<https://www.ncbi.nlm.nih.gov/pubmed/26463701>
412. Lucca, I., *et al.* Outcomes of minimally invasive simple prostatectomy for benign prostatic hyperplasia: a systematic review and meta-analysis. *World J Urol*, 2015. 33: 563.
<https://www.ncbi.nlm.nih.gov/pubmed/24879405>
413. Marshall, S.D., *et al.* Nocturia: Current Levels of Evidence and Recommendations From the International Consultation on Male Lower Urinary Tract Symptoms. *Urology*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25881866>
414. Cannon, A., *et al.* Desmopressin in the treatment of nocturnal polyuria in the male. *BJU Int*, 1999. 84: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/10444118>
415. Djavan, B., *et al.* The impact of tamsulosin oral controlled absorption system (OCAS) on nocturia and the quality of sleep: Preliminary results of a pilot study. *European Urology, Supplements*, 2005. 4: 1119.
[http://www.europeanurology.com/article/S1569-9056\(04\)00127-7/abstract/the-impact-of-tamsulosin-oral-controlled-absorption-system-ocas-on-nocturia-and-the-quality-of-sleep-preliminary-results-of-a-pilot-study](http://www.europeanurology.com/article/S1569-9056(04)00127-7/abstract/the-impact-of-tamsulosin-oral-controlled-absorption-system-ocas-on-nocturia-and-the-quality-of-sleep-preliminary-results-of-a-pilot-study)
416. Yokoyama, O., *et al.* Efficacy of fesoterodine on nocturia and quality of sleep in Asian patients with overactive bladder. *Urology*, 2014. 83: 750.
<https://www.ncbi.nlm.nih.gov/pubmed/24518285>
417. Yokoyama, O., *et al.* Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: impact on sleep evaluated by bladder diary. *J Urol*, 2011. 186: 170.
<https://www.ncbi.nlm.nih.gov/pubmed/21575976>
418. Johnson, T.M., 2nd, *et al.* The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia. *J Urol*, 2007. 178: 2045.
<https://www.ncbi.nlm.nih.gov/pubmed/17869295>

419. Oelke, M., *et al.* Impact of dutasteride on nocturia in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): a pooled analysis of three phase III studies. *World J Urol*, 2014. 32: 1141.
<https://www.ncbi.nlm.nih.gov/pubmed/24903347>
420. Oelke, M., *et al.* Effects of tadalafil on nighttime voiding (nocturia) in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a post hoc analysis of pooled data from four randomized, placebo-controlled clinical studies. *World J Urol*, 2014. 32: 1127.
<https://www.ncbi.nlm.nih.gov/pubmed/24504761>
421. Drake, M.J., *et al.* Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement. *J Urol*, 2004. 171: 1199.
<https://www.ncbi.nlm.nih.gov/pubmed/14767300>
422. Reynard, J.M., *et al.* A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. *Br J Urol*, 1998. 81: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/9488061>
423. Falahatkar, S., *et al.* Celecoxib for treatment of nocturia caused by benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled study. *Urology*, 2008. 72: 813.
<https://www.ncbi.nlm.nih.gov/pubmed/18692876>
424. Sigurdsson, S., *et al.* A parallel, randomized, double-blind, placebo-controlled study to investigate the effect of SagaPro on nocturia in men. *Scand J Urol*, 2013. 47: 26.
<https://www.ncbi.nlm.nih.gov/pubmed/23323790>

8. CONFLICT OF INTEREST

All members of the EAU Non-neurogenic Male LUTS Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: <http://www.uroweb.org/guidelines/>. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.



EAU Guidelines on Urinary Incontinence in Adults

F.C. Burkhard (Chair), J.L.H.R. Bosch, F. Cruz, G.E. Lemack,
A.K. Nambiar, N. Thiruchelvam, A. Tubaro,
Guidelines Associates: D. Ambühl, D. Bedretdinova, F. Farag,
B.B. Rozenberg

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1. INTRODUCTION

Urinary incontinence (UI) is an extremely common complaint in every part of the world. It causes a great deal of distress and embarrassment, as well as significant costs, to both individuals and societies. Estimates of prevalence vary according to the definition of incontinence and the population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost.

1.1 Aim and objectives

These Guidelines from the European Association of Urology (EAU) Working Panel on Urinary Incontinence are written by a multidisciplinary group, primarily for urologists, and are likely to be referred to by other professional groups. They aim to provide sensible and practical evidence-based guidance on the clinical problem of UI rather than an exhaustive narrative review. Such a review is already available from the International Consultation on Incontinence [1], and so the EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of UI. The focus of these Guidelines is entirely on assessment and treatment reflecting clinical practice. The Guidelines also do not consider patients with UI caused by neurological disease, or in children, as this is covered by complementary EAU Guidelines [2, 3].

The elderly

The Panel decided to include a separate but complimentary set of recommendations referring to the elderly population within each section. Older people with UI deserve special consideration for a number of reasons. Physiological changes with natural ageing mean that all types of UI become more common with increasing age. Urinary incontinence commonly co-exists with other comorbid conditions, reduced mobility, and impaired cognition and may require specific interventions, such as assisted toileting.

For the elderly person expectations of assessment and treatment may need to be modified to fit in with specific circumstances, needs, and preferences, while also taking into account any loss of capacity for consent. When the urologist is dealing with a frail elderly patient with urinary incontinence, collaboration with other healthcare professionals such as elderly care physicians is recommended.

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urinary Incontinence Panel consists of a multidisciplinary group of experts, including urologists, a gynaecologist and a physiotherapist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guideline/urinary-incontinence>.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Two scientific publications in the journal *European Urology* are also available [4, 5]. All documents are accessible through the EAU website: <http://www.uroweb.org/guideline/urinary-incontinence>.

1.4 Publication history

The EAU published the first Urinary Incontinence Guidelines in 2001. This 2017 publication presents a limited update of the 2016 Urinary Incontinence Guidelines.

1.4.1 Summary of changes.

Section 4.2 Pharmacological management has been revised for this 2017 print, including the addition of a new section 4.3.5.1 on Drug therapy.

Changed evidence summaries and recommendations can be found in sections:

4.2.1 *Antimuscarinic drugs*

Summary of evidence	LE
There is limited evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of urgency urinary incontinence.	1b
Higher doses of antimuscarinic drugs are more effective to cure or improve urgency urinary incontinence, but with a higher risk of side effects.	1b
Once daily (extended release) formulations are associated with lower rates of adverse events compared to immediate release ones, although similar discontinuation rates are reported in clinical trials.	1b
Dose escalation of antimuscarinic drugs may be appropriate in selected patients to improve treatment effect although higher rates of adverse events can be expected.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral antimuscarinic drugs, but has a high rate of withdrawal due to skin reaction.	1b

4.2.3.3 *Recommendations for antimuscarinic drugs*

Recommendations	GR
Offer antimuscarinic drugs for adults with urgency urinary incontinence who failed conservative treatment.	A
Consider extended release formulations in patients who do not tolerate immediate release antimuscarinics.	A
If antimuscarinic treatment proves ineffective, consider dose escalation or offering an alternative treatment.	B
Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.	B
Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence.	C

4.2.4 *Antimuscarinic agents: adherence and persistence*

Summary of evidence	LE
Adherence to antimuscarinic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost.	2
Most patients will stop antimuscarinic agents within the first three months.	2

4.2.5 *Antimuscarinic and beta3 agonist agents, the elderly and cognition*

Summary of evidence	LE
Antimuscarinic drugs are effective in elderly patients.	1b
Mirabegron has been shown to efficacious and safe in elderly patients.	1b
In older people, the cognitive impact of drugs which have anticholinergic effects is cumulative and increases with length of exposure.	2
Oxybutynin may worsen cognitive function in elderly patients.	2
Solifenacin, darifenacin, fesoterodine and trospium have been shown not to cause cognitive dysfunction in elderly people in short-term studies.	1b

4.2.5.2.13 *Additional recommendations for antimuscarinic drugs in the elderly*

Recommendations	GR
In older people being treated for urinary incontinence, every effort should be made to employ nonpharmacological treatments first.	C
Long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction.	B*
When prescribing antimuscarinic for urgency urinary incontinence, consider the total antimuscarinic load in older people on multiple drugs.	C
Consider the use of Mirabegron in elderly patients if additional antimuscarinic load is to be avoided.	C

*Recommendation based on expert opinion.

4.2.6 *Mirabegron*

Summary of evidence	LE
Mirabegron is better than placebo and as efficacious as antimuscarinics for improvement of urgency urinary incontinence symptoms.	1a
Adverse event rates with mirabegron are similar to placebo.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron than dose escalation of solifenacin.	1b

Recommendation	GR
In patients with urgency urinary incontinence and an inadequate response to conservative treatments, offer mirabegron unless they have uncontrolled hypertension.	A

4.2.7 *Drugs for stress urinary incontinence*

Summary of evidence	LE
Duloxetine, 40 mg twice daily improves stress urinary incontinence in women.	1a
Duloxetine causes significant gastrointestinal and central nervous system (CNS) side effects leading to a high rate of treatment discontinuation, although these symptoms are limited to the first weeks of treatment.	1a

Recommendations	GR
Duloxetine can be used with caution to treat women with symptoms of stress urinary incontinence.	A
Duloxetine should be initiated using dose titration because of high adverse event rates.	A

4.2.8 *Oestrogen*

Recommendation	GR
Vaginal oestrogen therapy for vulvovaginal atrophy should be prescribed long-term. In women with a history of breast cancer, the treating oncologist needs to be consulted.	C

4.2.9.2.2 Monitoring for hyponatraemia

Recommendations	GR
Consider offering desmopressin to patients requiring occasional short-term relief from daytime urinary incontinence and inform them that this drug is not licensed for this indication.	A
Monitor plasma sodium levels in patients on desmopressin.	A*

*Recommendation based on expert opinion.

4.2.10 *Drug treatment in mixed urinary incontinence*

Recommendation	GR
Offer antimuscarinic drugs or beta3 agonists to patients with urgency-predominant mixed urinary incontinence.	A*

*Recommendation based on expert opinion.

4.3.5.1 *Drug therapy*

Summary of evidence	LE
Duloxetine, either alone or combined with conservative treatment, can hasten recovery of continence but does not improve continence rate following prostate surgery.	1b

4.3.5.5 Compression devices in males

Recommendation	GR
Consider offering duloxetine to hasten recovery of continence after prostate surgery but inform the patient about the possible adverse events.	B

2. METHODS

2.1 Introduction

For the 2017 Urinary Incontinence Guidelines, the literature has been assessed for Section 4.2 – Pharmacological management. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between January 2012 and April 20th, 2016. A total of 1164 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <https://uroweb.org/guideline/urinary-incontinence/?type=appendices-publications>.

A systematic review was performed assessing nocturia and nocturnal incontinence in both men and women, in collaboration with the EAU Non-Neurogenic Male LUTS Guidelines Panel [6].

Due to the paucity of literature addressing nocturnal incontinence, the Panel did not include new information on this topic. The findings relating to nocturia in males are presented in the Non-Neurogenic Male LUTS Guidelines.

References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://www.uroweb.org/guideline/>. A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

The current Guidelines provide:

- A clear pathway (algorithm) for common clinical problems. This can provide the basis for thinking through a patient's management and also for planning and designing clinical services.
- A brief but authoritative summary of the current state of evidence on clinical topics, complete with references to the original sources.
- Clear guidance on what to do or not to do, in most clinical circumstances. This should be particularly helpful in those areas of practice for which there is little or no high-quality evidence.

In this edition the Panel has continued to focus, largely, on the management of a 'standard' patient. The Panel has referred in places to patients with 'complicated incontinence', by which we mean patients with associated morbidity, a history of previous pelvic surgery, surgery for UI, radiotherapy and women with associated genitourinary prolapse. An appendix is included on non-obstetric genitourinary fistulae. The subject of prevention of urinary incontinence has not been addressed. A systematic review on nocturnal incontinence found no studies on the topic. The Panel are of the opinion that nocturnal incontinence should be considered in future research studies.

2.2 Review

This document was subjected to peer review prior to publication in 2015. The decision for re-review is made based on the extent of the revision. A major revision resulting in significant changes to the clinical recommendations presented in the text will warrant re-review.

2.3 Terminology

Evidence summaries provide a succinct summary of what the currently available evidence tells us about an individual clinical question. They are presented according to the levels of evidence used by the EAU. Recommendations have been deliberately written as 'action-based' sentences. The following words or phrases are used consistently throughout the Guidelines;

- **Consider** an action. This word is used when there is not enough evidence to say whether the action causes benefit or risk to the patient. However, in the opinion of the Panel, the action may be justified in some circumstances. Action is optional.

- **Offer** an action. This word is used when there is good evidence to suggest that the action is effective, or that, in the opinion of the Panel, it is the best action. Action is advisable.
- **Carry out (perform)** an action. **Do** something. This phrase is used when there is strong evidence that this is the only best action in a certain clinical situation. Action is mandatory.
- **Do not perform** (i.e. avoid) an action. This phrase is used when there is high-level evidence that the action is either ineffective or is harmful to the patient. Action is contraindicated.

Future goals:

- An extended literature search revisiting the topic of female nocturia will be undertaken in collaboration with the Non-neurogenic male LUTS Guidelines Panel.
- An Algorithm for the management of nocturia in both males and females will be presented in the 2018 Urinary Incontinence Guidelines publication.

3. DIAGNOSTIC EVALUATION

3.1 History and physical examination

Taking a careful clinical history is fundamental to the clinical process. Despite the lack of formal evidence, there is universal agreement that taking a history should be the first step in the assessment of anyone with UI. The history should include details of the type, timing and severity of UI, associated voiding and other urinary symptoms. The history should allow UI to be categorised into stress urinary incontinence (SUI), urgency urinary incontinence (UUI) or mixed urinary incontinence (MUI). It should also identify patients who need rapid referral to an appropriate specialist. These include patients with associated pain, haematuria, a history of recurrent urinary tract infection (UTI), pelvic surgery (particularly prostate surgery) or radiotherapy, constant leakage suggesting a fistula, voiding difficulty or suspected neurological disease. In women, an obstetric and gynaecological history may help to understand the underlying cause and identify factors that may impact on treatment decisions. The patient should also be asked about other ill health and for the details of current medications, as these may impact on symptoms of UI.

Similarly, there is little evidence from clinical trials that carrying out a clinical examination improves care, but wide consensus suggests that it remains an essential part of assessment of people with UI. It should include abdominal examination, to detect an enlarged bladder or other abdominal mass, and perineal and digital examination of the rectum (prostate) and/or vagina. Examination of the perineum in women includes an assessment of oestrogen status and a careful assessment of any associated pelvic organ prolapse (POP). A cough test may reveal SUI if the bladder is sufficiently full while pelvic floor contraction together with urethral mobility can be assessed digitally.

3.2 Patient questionnaires

This section includes symptom scores, symptom questionnaires, scales, indexes, patient reported outcome measures (PROMs) and health-related quality of life (HRQoL) measures. The latter include generic or condition specific measures. Questionnaires should have been validated for the language in which they are being used, and, if used for outcome evaluation, must have been shown to be sensitive to change. The US Food and Drug Administration (FDA) published guidance for industry on patient-reported outcome instruments (questionnaires) in 2009 [8].

3.2.1 Questions

- In patients with UI, can the use of Questionnaires/PROMS differentiate between stress, urgency and mixed incontinence, and does this differentiation impact on quality of life (QoL) after treatment?
- In adults with UI, does assessment using either urinary symptom or QoL questionnaires improve treatment outcome for UI?
- In adults with UI, does assessment of the patient perspective (concerns or expectations) improve patient outcomes, regarding either urinary symptoms or QoL, compared to no patient-reported assessment?

3.2.2 Evidence

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs most of these studies did not include adult patients diagnosed with UI. This limits the extent to which results and conclusions from these studies can be applied in adults with UI. Some questionnaires (QUID, 3IQ) have potential to discriminate UI types in women [9, 10]. In men ICIQ-UI-SF score does not differentiate UI

types [11]. Some questionnaires are responsive to change and may be used to measure outcomes, though evidence on their sensitivity is inconsistent [12-14]. No evidence was found to indicate whether use of QoL or condition specific questionnaires have an impact on outcome of treatment.

Table 1 shows a summary of the ICUD review (2012) with recent additions. Criteria on which questionnaires are assessed include validity, reliability and responsiveness to change.

Table 1: Summary of the ICUD review 2012*.

	Category A (all 3 criteria fulfilled)*	Category B (2 criteria fulfilled)*	Category C (only 1 criterion fulfilled)*
Symptom measures and health-related QOL measures	ICIQ-UI Short Form, ICIQFLUTS, ICIQ-MLUTS IIQ and IIQ-7, I-QOL (ICIQ-Uqol), ISS, KHQ, LIS (?-interview), N-QoL, OAB-q SF, OAB-q (ICIQOABqol), PFDI and PFDI-20, PFIQ and PFIQ-7, PRAFAB, UISS	Contilife, EPIQ, LUTS tool IOQ, YIPS	ABSST ISI, ISQ, UIHI, UIQ
Measure of patient satisfaction (patient's measure of treatment satisfaction)	BSW, OAB-S, OABSAT-q, TBS	PPQ	EPI, GPI, PSQ
Goal attainment scales		SAGA	
Screening tools (used to identify patients with UI)	B-SAQ, OAB-SS, OABV8, OAB-V3, QUID	ISQ, USP 3IQ, CLSS, MESA, PUF	3IQ, CLSS, MESA, PUF
Patient symptom scale			
Assessment of symptom bother and overall bother	PPBC, UDI or UDI-6, LUSQ, PGI-I and PGI-S	PFBQ, SSI and SII	PMSES, POSQ, UI-4
Assessment of the impact of urgency	IUSS, U-IIQ, UU Scale, U-UDI	PPIUS, SUIQ, UPScore, UPScale, UQ, USIQ-QOL, USIQ-S, USS	
Questionnaires to assess sexual function and urinary symptoms		FSFI, ICIQ-VS, PISQ, SQoL-F	SFQ
Treatment adherence Measures		MASRI	

* For all abbreviations please see the Abbreviations list in the Appendix at the end of the full Guidelines.

** Criteria on which questionnaires are assessed include validity, reliability and responsiveness to change.

To date, there is no one questionnaire that fulfils all requirements for assessment of people with UI. Clinicians must evaluate the tools which exist, for use alone or in combination, for assessment and monitoring of treatment outcome [15].

The questionnaires can be found on the following websites: www.iciq.net, www.proqolid.org, www.mapi-institute.com, www.pfizerpatientreportedoutcomes.com, www.ncbi.nlm.nih.gov.

Summary of evidence	LE
Validated condition specific symptom scores assist in the screening for, and categorisation of, urinary incontinence.	3
Validated symptom scores measure the severity of urinary incontinence.	3
Both condition specific and general health status questionnaires measure current health status, and change following treatment.	3

Recommendation	GR
Use a validated and appropriate questionnaire when standardised assessment is required (See Table 1, above).	B*

* Recommendation based on expert opinion.

3.3 Voiding diaries

Measurement of the frequency and severity of LUTS is an important step in the evaluation and management of lower urinary tract (LUT) dysfunction, including UI. Voiding diaries are a semi-objective method of quantifying symptoms, such as frequency of UI episodes. They also quantify urodynamic variables, such as voided volume and 24-hour or nocturnal total urine volume. Voiding diaries are also known as micturition time charts, frequency/volume charts and bladder diaries.

Discrepancy between diary recordings and the patient rating of symptoms, e.g. frequency or UI, can be useful in patient counselling. In addition, voided volume measurement can be used to support diagnoses, such as overactive bladder (OAB) or polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials. In patients with severe UI, a voiding diary is unlikely to accurately report 24-hour urine output and so voided volume may be lower than total bladder capacity.

3.3.1 Question

- In adults with UI, what is the reliability, diagnostic accuracy and predictive value of a voiding diary compared to patient history or symptom score?

3.3.2 Evidence

Two articles have suggested a consensus has been reached in the terminology used in voiding [16, 17]. However, the terms micturition diary, frequency voiding chart and voiding diary, have been used interchangeably for many years and include information on fluid intake, times of voiding, voided volumes, incontinence episodes, pad usage, degree of urgency and degree of UI recorded for at least 24 hours. When reviewing the evidence all possible terminology has been included.

Two studies have demonstrated the reproducibility of voiding diaries in both men and women [18, 19]. Further studies have demonstrated variability of diary data within a 24-hour period and compared voided volumes recorded in diaries with those recorded by uroflowmetry [20, 21]. Another study found that keeping a voiding diary had a therapeutic benefit [22].

A number of observational studies have demonstrated a close correlation between data obtained from voiding diaries and standard symptom evaluation [23-26].

Summary of evidence	LE
Voiding diaries of three to seven days duration are a reliable tool for the objective measurement of mean voided volume, day time and night time frequency, and incontinence episode frequency.	2b
Voiding diaries are sensitive to change and are a reliable measure of outcome.	2b

Recommendations	GR
Ask patients with urinary incontinence to complete a voiding diary.	A
Use a diary duration of between three and seven days.	B

3.4 Urinalysis and urinary tract infection

Reagent strip ('dipstick') urinalysis may indicate urinary tract infection (UTI), proteinuria, haematuria or glycosuria requiring further assessment. Refer to the Urological Infections Guidelines for diagnosis and treatment of UTI [27].

3.4.1 Question

- In adults with UI, what is the diagnostic accuracy of urinalysis to detect UTI?
- In adults with UI does treatment of UTI or asymptomatic bacteriuria cure or improve UI compared to no treatment?

3.4.2 Evidence

Urinalysis negative for nitrite and leucocyte esterase reliably excludes UTI in people with UI [28] and should be included, with urine culture when necessary, in the evaluation of all patients with UI. Urinary incontinence may

occur during symptomatic UTI [29] and existing UI may worsen during UTI [30]. The rate and severity of UI was unchanged after eradication of asymptomatic bacteriuria in nursing home residents [31].

Summary of evidence	LE
Urinalysis negative for nitrite and leucocyte esterase reliably excludes urinary tract infection.	1
Urinary incontinence may be a symptom during urinary tract infection.	3
The presence of a symptomatic urinary tract infection worsens symptoms of urinary incontinence.	3
Elderly nursing home patients with urinary incontinence do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	GR
Perform urinalysis as a part of the initial assessment of a patient with urinary incontinence.	A*
If a symptomatic urinary tract infection is present with urinary incontinence, reassess the patient after treatment.	A*
Do not routinely treat asymptomatic bacteriuria in elderly patients to improve urinary incontinence.	B

* Recommendation based on expert opinion.

3.5 Post-void residual volume

Post-void residual (PVR) volume is the amount of urine that remains in the bladder after voiding. It indicates poor voiding efficiency, which may result from a number of contributing factors. It is important because it may worsen symptoms and, more rarely, may be associated with UTI, upper urinary tract (UUT) dilatation and renal insufficiency. Both bladder outlet obstruction and detrusor underactivity contribute to the development of PVR. Post-void residual can be measured by catheterisation or ultrasound (US). The prevalence of PVR in patients with UI is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume.

3.5.1 Question

In adults with UI, what is the value of measuring PVR?

3.5.2 Evidence

Most studies investigating PVR have not included patients with UI. Although some studies have included women with UI and men and women with LUTS, they have also included children and adults with neurogenic UI. In general, the data on PVR can be applied with caution to adults with non-neurogenic UI. The results of studies investigating the best method of measuring PVR [32-37] have led to the consensus that US measurement of PVR is preferable to catheterisation.

In peri- and post-menopausal women without significant LUTS or pelvic organ symptoms, 95% of women had a PVR < 100 mL [38]. In women with UUI, a PVR > 100 mL was found in 10% of cases [39]. Other research has found that a high PVR is associated with POP, voiding symptoms and an absence of SUI [38, 40-42].

In women with SUI, the mean PVR was 39 mL measured by catheterisation and 63 mL measured by US, with 16% of women having a PVR > 100 mL [39].

Summary of evidence	LE
Lower urinary tract symptoms coexisting with Urinary incontinence are associated with a higher rate of post-void residual compared to asymptomatic subjects.	2

Recommendations	GR
When measuring post-void residual urine volume, use ultrasound.	A
Measure post-void residual in patients with urinary incontinence who have voiding symptoms.	B
Measure post-void residual when assessing patients with complicated urinary incontinence.	C
Post-void residual should be monitored in patients receiving treatments that may cause or worsen voiding dysfunction, including surgery for stress urinary incontinence.	A*

* Recommendation based on expert opinion.

3.6 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, in the belief that it may help to provide or confirm diagnosis, predict treatment outcome, or facilitate discussion during counselling. For all these reasons, urodynamics is often performed prior to invasive treatment for UI. These Guidelines will focus on invasive tests, including multichannel cystometry, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry, Valsalva leak point pressure estimation, and retrograde urethral resistance measurement.

3.6.1 Question

In adults with UI, what is the reproducibility, diagnostic accuracy and predictive value of urodynamic testing?

3.6.2 Evidence

3.6.2.1 Variability

In common with most physiological tests there is variability in urodynamics results. A number of small studies, assessing same-session repeatability of urodynamic testing, present contradictory findings [43, 44]. Measurement of urethral closure pressure (MUCP) correlates poorly with incontinence severity [45] and there is conflicting evidence about its reproducibility [46, 47]. One method of recording MUCP cannot be compared meaningfully to another [48].

Valsalva leak point pressures are not standardised and there is minimal evidence about reproducibility. Valsalva leak point pressure did not reliably assess incontinence severity in a cohort of women selected for surgical treatment of SUI [49]. The predictive value of the tests, regarding the outcome of treatment, remains unclear. No studies on the reproducibility of ambulatory monitoring were found.

3.6.2.2 Diagnostic accuracy

The diagnostic accuracy of urodynamics is assessed in terms of its correlation with clinical diagnosis of UI and incontinence severity. The problem is that clinical diagnosis and urodynamic findings often do not correlate [50, 51], and normal healthy people may have urodynamic abnormalities.

The diagnostic accuracy of urethral pressure profilometry [45] and 'urethral retro-resistance' is generally poor [52]. Urethral reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [53].

Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry, but the clinical relevance of this is uncertain [54, 55].

3.6.2.3 Question

Does urodynamics influence the outcome of conservative therapy?

3.6.2.4 Evidence

A Cochrane review of seven RCTs showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery. However, there was no evidence that this influence on decision making altered the clinical outcome of treatment [56]. Subanalysis of an RCT comparing fesoterodine to placebo [57, 58] showed no predictive value for treatment response, by the urodynamic diagnosis of detrusor overactivity (DO).

3.6.2.5 Question

Does urodynamics influence the outcome of surgery for urinary incontinence?

3.6.2.6 Evidence

A high-quality RCT (n = 630) compared office evaluation alone to office evaluation and urodynamics in women with clinical demonstrable SUI about to undergo surgery for SUI. Whilst urodynamics changed the clinical diagnosis in 56% of women [59], there was no difference in levels of UI or any secondary outcome at twelve months follow-up after surgery [60]. Another similar study closed with only 59 women included due to recruitment problems, found that the omission of urodynamics was not inferior in the pre-operative work up of SUI [61]. This study was then redesigned so that patients in whom urodynamics were discordant with clinical assessment (n = 109) were randomly allocated to receive either immediate surgery or individually tailored therapy based on urodynamics. In this trial, performing immediate surgery, irrespective of the result of urodynamics, did not result in inferior outcomes [62].

In observational studies there is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery [24-27]. The same is true for a secondary analysis of an RCT [63].

Augmentation cystoplasty is only performed in patients with a urodynamic diagnosis of DO, so no statement can be made about predictive value for this group [58].

The Panel recognise that it may be valuable to use urodynamic test results to select the optimum surgical procedure but, at the time of this review, there is inconsistent evidence regarding any predictive value that would support this approach.

3.6.2.7 Question

Does urodynamics help to predict complications of surgery for UI?

3.6.2.8 Evidence

There have been no RCTs designed to answer this question.

The presence of pre-operative DO has been associated with post-operative UUI, but did not predict overall treatment failure following mid-urethral sling [63] or following sling surgery or colposuspension.

Whilst low pre-operative flow rate has been shown to correlate with post-operative voiding dysfunction [64, 65], post hoc analysis of two high-quality surgical trials showed that no pre-operative urodynamic parameter had the ability to predict post-operative voiding dysfunction in a selected population of women with low pre-operative PVR [66, 67].

3.6.2.9 Question

Does urodynamics influence the outcome of treatment for post-prostatectomy urinary incontinence in men?

3.6.2.10 Evidence

There are no RCTs examining the clinical usefulness of urodynamics in post-prostatectomy UI. Whilst urodynamics will distinguish causes of incontinence, its ability to predict outcome of surgery for incontinence for these men is uncertain [68, 69].

Summary of evidence	LE
Most urodynamic parameters show variability within the same session and over time, and this limits their clinical usefulness.	3
Different techniques of measuring urethral function may have good test-retest reliability, but do not consistently correlate to other urodynamic tests or to the severity of urinary incontinence.	3
There is limited evidence that ambulatory urodynamics is more sensitive than conventional urodynamics for diagnosing stress urinary incontinence or detrusor overactivity.	2
There may be inconsistency between history and urodynamic results.	3
Preliminary urodynamics can influence the choice of treatment for urinary incontinence, but does not affect the outcome of conservative therapy or drug therapy for stress urinary incontinence.	1a
Pre-operative urodynamics in women with uncomplicated, clinically demonstrable stress urinary incontinence does not improve the outcome of surgery for stress urinary incontinence.	1b
There is no consistent correlation between the result of urethral function tests and subsequent success or failure of stress urinary incontinence surgery.	3
There is no consistent evidence that pre-operative detrusor overactivity is associated with surgical failure of mid-urethral sling in women.	3
The presence of pre-operative detrusor overactivity may be associated with persistence of urgency post-operatively.	3
There is no evidence that urodynamics predicts the outcomes of treatment for post-prostatectomy incontinence in men.	4

Recommendations	GR
<i>(NB: Concerning only neurologically intact adults with urinary incontinence)</i>	
Clinicians carrying out urodynamics in patients with urinary incontinence should: <ul style="list-style-type: none"> ensure that the test replicates the patient's symptoms; interpret results in the context of the clinical problem; check recordings for quality control; remember there may be physiological variability within the same individual. 	C
Advise patients that the results of urodynamics may be useful in discussing treatment options, although there is limited evidence that performing urodynamics will predict the outcome of treatment for uncomplicated urinary incontinence.	C
Do not routinely carry out urodynamics when offering treatment for uncomplicated urinary incontinence.	B
Perform urodynamics if the findings may change the choice of invasive treatment.	B
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence or predict the outcome of treatment.	C
Urodynamic practitioners should adhere to standards defined by the International Continence Society.	C

3.6.3 **Research priority**

Does any individual urodynamic test, or combination of tests, influence the choice of treatments or prediction of treatment outcome for UI?

3.7 **Pad testing**

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of UI, as well as a patient's response to treatment.

3.7.1 **Questions**

- In adults with UI, what is the reliability, diagnostic accuracy and predictive value of pad testing?
- In adults with UI, is one type of pad test better than another?

3.7.2 **Evidence**

The clinical usefulness of pad tests for people with UI has been assessed in two systematic reviews [70, 71]. A one-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g shows good specificity but lower sensitivity for symptoms of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise with variation according to activity level [72]. Pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated or the degree of provocation increased [73]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [70, 74] although early post-operative testing may predict future continence in men after prostatectomy [75]. Pad test is responsive to change following successful treatment [76]. There is no evidence that one type of pad test is superior to another.

Summary of evidence	LE
A pad test can diagnose urinary incontinence accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	2
Change in leaked urine volume on pad tests can be used to measure treatment outcome.	2

Recommendations	GR
Have a standardised duration and activity protocol for pad test.	B
Use a pad test when quantification of urinary incontinence is required.	C
Use repeat pad test after treatment if an objective outcome measure is required.	C

3.7.3 **Research priority**

- Do the results of pad testing influence the choice of treatments or the prediction of the outcome of treatment for UI?
- Does the amount of physical activity influence the outcome of 24-hour pad testing leading to overestimation of the severity of incontinence?

3.8 Imaging

Imaging improves our understanding of the anatomical and functional abnormalities that may cause UI. In clinical research, imaging is used to understand the relationship between anatomy and function, between conditions of the central nervous system (CNS) or of the lower urinary tract (LUT) and UI, and to investigate the relationship between LUT and pelvic floor imaging and treatment outcome.

Ultrasound and magnetic resonance imaging (MRI) have largely replaced X-ray imaging. Ultrasound is preferred to MRI because of its ability to produce three-dimensional and four-dimensional (dynamic) images at lower cost and wider availability. Studies on LUT imaging in patients with UI often include an evaluation of surgical outcomes, making design and conduct of these trials challenging.

3.8.1 Questions

In adults with UI:

- What is the reliability and accuracy of imaging in the diagnosis of UI?
- Do the results of imaging influence the choice of treatment for UI?
- Do the results of imaging help predict outcome of treatment for UI?
- Do the results of imaging help evaluate outcome of treatments for UI?

3.8.2 Evidence

Many studies have evaluated the imaging of bladder neck mobility by US and MRI, and concluded that UI cannot be identified by a particular pattern of urethrovesical movements [77]. In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with *de novo* SUI [78].

There is a general consensus that MRI provides good global pelvic floor assessment, including POP, defecatory function and integrity of the pelvic floor support [79]. However, there is a large variation in MRI interpretation between observers [80] and little evidence to support its clinical usefulness in the management of UI.

Studies have assessed the use of imaging to assess the mechanism of mid-urethral sling insertion for SUI. One study suggested that mid-urethral sling placement decreased mobility of the mid-urethra but not mobility of the bladder neck [81]. Following mid-urethral sling, a wider gap between symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [82].

Several imaging studies have investigated the relationship between sphincter volume and function in women [83] and between sphincter volume and surgery outcome, in men and women [84, 85]. In patients undergoing radical prostatectomy, longer membranous urethra before and after surgery was associated with a higher rate of continence [86]. However, no imaging test has been shown to predict the outcome of treatment for UI. Imaging of the pelvic floor can identify *levator ani* detachment and hiatus size, although there is little evidence of a relationship to clinical benefit after treatment of UI.

Detrusor wall thickness

As overactive bladder syndrome (OAB) has been linked to detrusor over-activity, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). However, there is no evidence that BWT/DWT imaging improves management of OAB in practice. No consensus exists as to the relationship between OAB and increased BWT/DWT [87].

Summary of evidence	LE
Imaging can reliably be used to measure bladder neck and urethral mobility, although there is no evidence of clinical benefit for patients with urinary incontinence.	2b
There is no consistent evidence that bladder (detrusor) wall thickness measurement is useful in the management of urinary incontinence.	3

Recommendation	GR
Do not routinely carry out imaging of the upper or lower urinary tract as part of the assessment of urinary incontinence.	A

3.8.3 Research priority

More research is needed into the relationship between sling position, as determined by imaging, and surgical outcome.

4. DISEASE MANAGEMENT

4.1 Conservative management

In clinical practice, it is the convention that non-surgical therapies are tried first because they usually carry the least risk of harm. They are often used in combination which makes it difficult to determine which components are effective. Containment devices play an important role, especially for individuals who prefer to avoid the risks of interventional treatments, or in whom active treatment is impossible for any reason.

4.1.1 Simple clinical interventions

4.1.1.1 Underlying disease/cognitive impairment

Urinary incontinence, especially in the elderly, has been associated with multiple comorbid conditions including:

- cardiac failure;
- chronic renal failure;
- diabetes;
- chronic obstructive pulmonary disease;
- neurological disease including stroke and multiple sclerosis;
- general cognitive impairment;
- sleep disturbances, e.g. sleep apnoea;
- depression;
- metabolic syndrome.

It is possible that improvement of associated disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients frequently suffer from more than one condition. In addition, interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's UI.

4.1.1.1.1 Question

In adults with UI, does improving an associated condition improve UI compared to no correction of that condition?

4.1.1.1.2 Evidence

There is compelling evidence that there is a higher prevalence of UI in women with type 2 diabetes. One study showed no correlation between earlier intensive treatment of type 1 diabetes mellitus and the prevalence of UI in later life vs. conventional treatment [88].

Summary of evidence	LE
There is a lack of evidence that improving any associated condition improves urinary incontinence, with the exception of weight loss (see section 4.1.2.4 Obesity and weight loss).	3

Recommendation	GR
Patients with urinary incontinence who have associated conditions, should have appropriate treatment for those conditions in line with good medical practice.	A*

* Recommendation based on expert opinion.

4.1.1.2 Adjustment of other (non-incontinence) medication

Although UI is listed as an adverse effect of many drugs in drug compendia, this mainly results from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies have used the occurrence of UI as a primary outcome, or were powered to assess the occurrence of statistically significant UI, or worsening rates against placebo. In most cases, it is therefore not possible to be sure that a drug causes UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, comorbidity or ageing on UI. Although changing drug regimens for underlying disease may be considered as a possible early intervention for UI, there is very little evidence of benefit [50]. There is also a risk that stopping or altering medication may result in more harm than benefit.

4.1.1.2.1 Question

In adults with UI, does adjustment of other (non-incontinence) medication improve UI compared to no change in treatment?

4.1.1.2.2 Evidence

Structured literature review failed to identify any studies addressing whether adjustment of specific medications could alter existing symptoms of UI. Also, there is little evidence relating to the occurrence or worsening of UI in relation to prescription of any specific drugs.

Summary of evidence	LE
There is very little evidence that alteration of non-incontinence medication can cure or improve symptoms of urinary incontinence.	3

Recommendations	GR
Take a drug history from all patients with urinary incontinence.	A
Review any new medication associated with the development or worsening of urinary incontinence.	C

4.1.1.3 Constipation

Several studies have shown strong associations between constipation and UI. Constipation can be improved by behavioural, physical and medical treatments.

4.1.1.3.1 Question

Does treatment for constipation improve UI?

4.1.1.3.2 Evidence

Two, large, cross-sectional population-based studies [89, 90] and two longitudinal studies [91, 92] showed that constipation was a risk factor for LUTS. An observational study comparing women with UI and women with pelvic organ prolapse (POP) to controls found that a history of constipation was associated with both prolapse and UI [93]. One RCT found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc., reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both [94].

In conclusion, constipation appears to be associated with UI. However, there is no evidence to show whether or not treating constipation improves UI, although both constipation and UI appear to be improved by certain behavioural interventions.

Summary of evidence	LE
There is a consistent association between a history of constipation and the development of urinary incontinence and pelvic organ prolapse.	3
There is no consistent evidence in adults that treatment of constipation alone improves urinary incontinence.	4

Recommendation	GR
Adults with urinary incontinence who also suffer from constipation should be given advice about bowel management in line with good medical practice.	C

4.1.1.3.3 Research priority

Does the normalisation of bowel habit improve UI in patients who are constipated?

4.1.1.4 Containment

Containment is important for people with UI when active treatment does not cure the problem, or when it is not available or not possible. Some individuals may prefer containment rather than undergo active treatment with its associated risks. This includes the use of absorbent pads, urinary catheters, external collection devices, penile clamps for men and intravaginal devices for women. Studies of catheter use are not specific to patients with non-neurogenic UI. Detailed literature summaries can be found in the current ICUD monograph [1] and in European Association of Urological Nurses guidance documents [95-97]. A useful resource for health care professionals and patients can be found at: www.continenceproductadvisor.org.

4.1.1.4.1 Question

For adults with UI, is one type of containment device better than another?

4.1.1.4.2 Evidence

One RCT involving elderly women in care comparing management with pads to indwelling urethral catheter found no difference in dependency level or skin integrity score at six months [98]. Use of an external sheath was compared with indwelling catheterisation over 30 days in an RCT involving elderly men resident in hospital [99]; there were no differences in bacteriuria or symptomatic UTI but the sheath was more comfortable. A short-term (two weeks) crossover RCT in men with UI found that disease specific QoL was better when using an external sheath and more men preferred it, compared to pads [100].

4.1.1.4.3 Question

For men or women with UI, is one type of pad better than another?

4.1.1.4.4 Evidence

A systematic review of six RCTs comparing different types of pads found that pads filled with superabsorbent material were better than standard pads, whilst evidence that disposable pads were better than washable pads was inconsistent [101]. For men with light UI, a randomised crossover trial found that a leaf-shaped type of pad was preferred to rectangular pads [102]. A series of three crossover RCTs examined performance of different pad designs for differing populations [103]. For women with light UI, disposable insert pads (within washable pouch pants) were most effective. In adults with moderate/severe incontinence, disposable pull-up pants were more effective for women, whilst for men disposable diapers were more effective during the day and washable diapers at night.

4.1.1.4.5 Question

For men or women with UI, is one type of catheter or external collection device better than another?

4.1.1.4.6 Evidence

A Cochrane review summarised three RCTs comparing different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [104]. A systematic review of non-randomised studies found no differences in UTI outcome or UUT changes between use of suprapubic or urethral catheter drainage; however, patients with suprapubic catheters were less likely to have urethral complications [105]. For people using intermittent catheterisation, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [106]. However, there is recent evidence from a narrative review suggesting that in certain populations using single-use catheters may reduce urethral trauma and UTI [107]. A Cochrane review summarising five trials comparing washout policies in adults with indwelling urinary catheters found inconsistent evidence of benefit [108].

A further Cochrane review summarising eight trials testing whether antibiotic prophylaxis was beneficial for adults using intermittent or indwelling catheterisation found it reduced incidence of symptomatic UTI but possible harms were not assessed [109].

4.1.1.4.7 Question

For men and women with UI, are external pressure devices more effective than standard treatment and is one device better than another?

4.1.1.4.8 Evidence

A crossover RCT in twelve men with post-prostatectomy incontinence found a hinge-type penile clamp to be more effective than circular clamps for control of UI and that the hinge-type penile clamp was preferred by participants, although it reduced penile blood flow [110].

A Cochrane review summarised seven trials comparing mechanical devices in women with UI finding limited evidence that SUI was reduced by intravaginal devices, no evidence on the effectiveness of intra-urethral devices, and that there was no difference in control of UIs between intravaginal and intra-urethral devices [111]. There was no difference in outcome at twelve months in women with SUI between vaginal pessary alone; pelvic floor muscle training (PFMT) alone; and vaginal pessary + PFMT, although vaginal pessary was inferior to PFMT at three months for both from UI.

Summary of evidence	LE
Pads are effective in containing urine.	1b
Hinge-type penile clamps are more effective than circular clamps to control stress urinary incontinence in men.	2a
Vaginal devices may improve stress urinary incontinence in women in selective groups.	2a

Recommendations	GR
Ensure that adults with urinary incontinence and/or their carers are informed regarding available treatment options before deciding on containment alone.	A*
Suggest use of disposable insert pads for women and men with light urinary incontinence.	A*
In collaboration with other healthcare professionals with expertise in urinary incontinence, help adults with moderate/severe urinary incontinence to select the individually best containment regimen considering pads, external devices and catheters, balancing benefits and harms.	A*
Choice of pad, from the wide variety of different absorbent materials and designs available, should be made with consideration of the individual patient's circumstance, degree of incontinence and preference.	B

* Recommendation based on expert opinion.

4.1.1.4.9 Research priority

To develop methods for assessing the best method of containment for individual adults with UI.

4.1.2 Lifestyle interventions

Examples of lifestyle factors that may be associated with incontinence include obesity, smoking, level of physical activity and diet. Modification of these factors may improve UI.

4.1.2.1 Caffeine reduction

Many drinks contain caffeine, particularly tea, coffee and cola. Anecdotal evidence of urinary symptoms being aggravated by excessive caffeine intake has focused attention on whether caffeine reduction may improve UI. However, a cross-sectional population survey found no statistical association between caffeine intake and UI [112]. Lack of knowledge about the caffeine content of different drinks has made the role of caffeine reduction in alleviating UI difficult to assess.

4.1.2.1.1 Question

In adults with UI, does caffeine reduction improve UI or QoL compared to no caffeine reduction?

4.1.2.1.2 Evidence

Four studies were found on the effect of caffeine reduction on UI [113-116]. They were of moderate quality and the results were inconsistent. The studies were mainly in women, so results can only be cautiously generalised to men [114, 115]. One RCT showed that reducing caffeine intake as an adjunct to behavioural therapy resulted in reduced urgency but not reduced UI compared to behavioural therapy alone [114]. Another RCT found that reducing caffeine had no benefit for UI [115]. A further interventional study in the elderly showed borderline significance for the benefit of reducing caffeine intake on UI [116]. In a large prospective cohort study there was no evidence that caffeine reduction reduced the risk of progression of UI over two years [117].

Summary of evidence	LE
Reduction of caffeine intake does not improve urinary incontinence.	2
Reduction in caffeine intake may improve symptoms of urgency and frequency.	2

4.1.2.2 Physical exercise

Regular physical activity may strengthen the pelvic floor musculature and possibly decrease the risk of developing UI, especially SUI. However, it is also possible that heavy physical exercise may aggravate UI.

4.1.2.2.1 Question

Does physical exercise cause, improve or exacerbate UI in adults?

4.1.2.2.2 Evidence

The association between exercise and UI is unclear. Four studies [112, 118-120] in differing populations concluded that strenuous physical exercise increases the risk of SUI during periods of physical activity. There is also consistent evidence that physically active females and elite athletes experience higher levels of SUI than control populations [121-126]. On the other hand, the presence of UI may prevent women from taking exercise [127]. There is no evidence that strenuous exercise predisposes athletes to the development of SUI later in life [128]. Lower levels of UI have been observed in cohorts of women who undertake moderate exercise, but it remains unclear whether taking exercise can prevent development of UI [129, 130].

The elderly

Three RCTs in the elderly confirmed that exercise, as a component of a multidimensional regime including PFMT and weight loss, was effective in improving UI in women. It is not clear which component of such a scheme is most important [94, 131, 132].

Summary of evidence	LE
Female athletes may experience urinary incontinence during intense physical activity but not during common activities.	3
Strenuous physical activity does not predispose for women to urinary incontinence later in life.	3
Moderate exercise is associated with lower rates of urinary incontinence in middle-aged or older women.	2b

4.1.2.3 Fluid intake

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with UI to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that low or high 24-hour urine output should be investigated.

4.1.2.3.1 Question

In adults with UI, what is the effect of modifying fluid intake compared to not modifying fluid intake on symptoms and QoL?

4.1.2.3.2 Evidence

The few RCTs [115, 133, 134] provide inconsistent evidence. In most studies, the instructions for fluid intake were individualised and it is difficult to assess participant adherence to protocol. All available studies were in women. An RCT [134] showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving antimuscarinics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice [135].

Summary of evidence	LE
There is conflicting evidence on whether fluid modification improves urinary incontinence.	2

4.1.2.4 Obesity and weight loss

Being overweight or obese has been identified as a risk factor for UI in many epidemiological studies [136, 137]. There is evidence that the prevalence of both UUI and SUI increases proportionately with rising body mass index [138]. The proportion of patients who undergo surgery for incontinence who are overweight or obese is higher than that of the general population [139].

4.1.2.4.1 Question

In adults with UI, does weight loss lead to an improvement in symptoms of UI or QoL?

4.1.2.4.2 Evidence

All the available evidence relates to women. Three systematic reviews plus two large RCTs concluded that weight loss was beneficial in improving UI [136, 137, 140]. Five further RCTs reported a similar beneficial effect on incontinence following surgical weight reduction programmes [141-144]. Two large studies in women with diabetes, for whom weight loss was the main lifestyle intervention, showed UI did not improve but there was a lower subsequent incidence of UI among those who lost weight [141, 145]. There have been other cohort studies and case-control studies suggesting similar effects, including surgery for the morbidly obese [146-150].

Summary of evidence	LE
Obesity is a risk factor for urinary incontinence in women.	1b
Non-surgical weight loss in overweight and obese women improves urinary incontinence.	1a
Surgical weight loss improves urinary incontinence in obese women.	1b
Weight loss in obese women improves urinary incontinence.	1b
Weight loss in obese adults with diabetes mellitus reduces the risk of developing urinary incontinence.	1b

4.1.2.5 Smoking

Smoking cessation is now a generalised public health measure and has been shown to be weakly associated with improving urgency frequency and UI [112, 151].

4.1.2.5.1 Question

In adults with UI, does smoking cessation improve patient outcomes regarding either urinary symptoms or QoL compared to continued smoking?

4.1.2.5.2 Evidence

The effect of smoking cessation on UI was described as uncertain in a NIHR review [152].

Summary of evidence	LE
There is no evidence that smoking cessation will improve the symptoms of urinary incontinence.	4

4.1.2.6 Recommendations for lifestyle interventions

Recommendations	GR
Encourage obese women with urinary incontinence to lose weight and maintain weight loss.	A
Advise adults with urinary incontinence that reducing caffeine intake may improve symptoms of urgency and frequency but not incontinence.	B
Patients with abnormally high or abnormally low fluid intake should be advised to modify their fluid intake appropriately in line with good medical practice.	C
Counsel female athletes experiencing urinary incontinence with intense physical activity that it will not predispose them to urinary incontinence in later life.	C
Patients with urinary incontinence who smoke should be given smoking cessation advice in line with good medical practice.	A

4.1.2.7 Research priority

Which lifestyle modifications are effective for the cure or sustained improvement of UI?

4.1.3 Behavioural and Physical therapies

Terminology relating to behavioural and physical therapies remains confusing because of the wide variety of ways in which treatment regimens and combinations of treatments have been delivered in different studies [153]. The terms are used to encompass all treatments which require a form of self-motivated personal retraining by the patient and also include techniques which are used to augment this effect.

Approaches include bladder training (BT) and pelvic floor muscle training (PFMT), but terms such as bladder drill, bladder discipline and bladder re-education and behaviour modification are also used. Almost always in clinical practice, these will be introduced as part of a package of care including lifestyle changes, patient education and possibly some cognitive therapy as well. The extent to which individual therapists motivate, supervise and monitor these interventions is likely to vary but it is recognised that these influences are important components of the whole treatment package.

4.1.3.1 Prompted voiding

The term 'prompted voiding' implies that carers, rather than the patient, initiate the decision to void and this applies largely to an assisted care setting.

Two systematic reviews (nine RCTs) [154, 155] confirmed a positive effect on continence outcomes for prompted voiding in comparison to standard care [155]. Timed voiding is defined as fixed, pre-determined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding reviewed two RCTs, finding inconsistent improvement in continence compared with standard care in cognitively impaired adults [156].

4.1.3.2 Bladder Training

Bladder training (also referred to in the past as bladder drill, bladder discipline, bladder re-education, bladder retraining): A programme of patient education along with a scheduled voiding regimen with gradually adjusted voiding intervals. Specific goals are to correct faulty habit patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes and restore

patient confidence in controlling bladder function. The ideal form or intensity of a BT programme for UI is unclear. It is also unclear whether or not BT can prevent the development of UI.

4.1.3.2.1 Questions

In adults with UI:

- Is BT better than no treatment for cure or improvement of UI?
- Is BT better than other conservative treatments for cure or improvement of UI?
- Does BT, as an adjunct to other conservative treatments, cure or improve UI?
- Are the benefits of BT durable in the longer term?
- Are there any patient groups for whom BT is more effective?

4.1.3.2.2 Evidence

There have been three systematic reviews on the effect of BT compared to standard care [50, 152, 157] confirming that BT is more effective than no treatment in improving UUI. The addition of BT to anticholinergic therapy did not improve UI compared to antimuscarinics alone but it did improve frequency and nocturia [158].

This review identified seven RCTs in which BT was compared to drug therapy alone and showed only a benefit for oxybutynin in cure and improvement of UI [158].

Bladder training alone is inferior to a high-intensity programme of PFMT to improve SUI in elderly women [159]. Bladder training is better than intravaginal pessaries to control SUI, although the improvement may only be short term. Whatever the method of training used, any benefit of BT on UI is likely to be of short duration unless the BT programme is practised repeatedly. No adverse events have been reported with BT. Biofeedback combined with BT increased continence rates and improved MUI in two RCTs [157].

Summary of evidence	LE
Bladder training is effective for improvement of urinary incontinence in women.	1b
The effectiveness of bladder training diminishes after the treatment has ceased.	2
The comparative benefit of bladder training and drugs for the improvement of urgency urinary incontinence remains uncertain.	2
The combination of bladder training with antimuscarinic drugs does not result in greater improvement of urinary incontinence but may improve frequency and nocturia.	1b
Bladder training is better than pessary alone.	1b
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b

For recommendations see section 4.1.3.5.

4.1.3.3 Pelvic floor muscle training (PFMT)

Pelvic floor muscle training is used to improve function of the pelvic floor, improving urethral stability. There is some evidence that improving pelvic floor function may inhibit bladder contraction in patients with OAB [160]. Pelvic floor muscle training may be used to prevent UI, e.g. in childbearing women before birth, in men about to undergo radical prostatectomy, or as part of a planned recovery programme after childbirth or surgery. Most often, PFMT is used to treat existing UI, and may be augmented with biofeedback (using visual, tactile or auditory stimuli), surface electrical stimulation or vaginal cones.

4.1.3.3.1 Question

In adult men and women suffering from UI, does treatment with PFMT, given either alone or augmented with biofeedback, electrical stimulation or vaginal cones, improve or cure UI or improve QoL, compared to no treatment, sham treatment or other conservative treatments, e.g. bladder training, electrical stimulation or vaginal cones?

4.1.3.3.2 Evidence

In a recent UK Health Technology Appraisal (HTA), the role of PFMT in the care of women with SUI was analysed in a direct comparison of treatments using a mixed treatment comparison model, which compared different 'packages' of care [152]. This extensive meta-analysis reviewed data from 37 interventions and 68 direct comparisons, while the mixed treatment comparisons examined combinations of fourteen different types of intervention from 55 separate trials. The mixed treatment comparison used both indirect and direct comparisons and may provide more accurate estimates of effect. Where relevant, the Health Technology Appraisal has influenced the evidence and recommendations in these Guidelines. The Agency for Healthcare

Research and Quality (AHRQ) review of nonsurgical treatment of UI in adult women also included indirect comparison methods as well as conventional meta-analysis [157].

4.1.3.3.3 Efficacy of PFMT in SUI, UUI and MUI in women

This question has been addressed by several systematic reviews [152, 157, 161], all report inconsistency between studies because of poor reporting of technique and different outcome measures. Meta-analysis showed that PFMT was effective for cure or improvement of incontinence, and improvement in QoL. The effect applies in women with SUI, UUI and MUI though the effect in MUI is lower than in women with pure SUI. A Cochrane review comparing different approaches to delivery of PFMT (21 RCTs) concluded that increased intensity of delivery of the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions [162]. No other consistent differences between techniques were found.

With regard to the durability of PFMT, another RCT reported fifteen-year follow-up outcomes of an earlier RCT, showing that long-term adherence to treatment was poor and half of patients had progressed to surgery [163]. Numerous systematic reviews have addressed the question of whether the effects of PFMT and BT are additive [152, 157, 164]. These reviews are confounded by differences in patient selection and have arrived at conflicting conclusions leaving uncertainty about the extent to which one treatment may augment the other. Similarly, there remains uncertainty about the additional value of biofeedback with systematic reviews reaching differing conclusions [157, 164].

Comparison of PFMT to other treatments was extensively reviewed by both AHRQ and the 2010 UK HTA [152, 157], which considered additional non-randomised data as part of a mixed treatment comparison. The UK HTA resulted in a number of different findings from those based solely on direct comparisons. In conclusion, the HTA, using a revised methodology, supporting the general principle that greater efficacy was achieved by adding together different types of treatment and by increasing intensity.

Efficacy of PFMT in childbearing women

Two systematic reviews [165, 166] reviewed RCTs in pregnant or postpartum women, which included PFMT in one arm of the trial. Treatment of UI with PFMT in the postpartum period increased the chances of continence at 12 months' postpartum.

4.1.3.3.4 PFMT in the elderly

The effect of PFMT in women with SUI does not seem to decrease with increased age: in trials with older women with SUI it appeared both primary and secondary outcome measures were comparable to those in trials focused on younger women [131, 159, 167].

4.1.3.3.5 PFMT and Radical prostatectomy

A 2015 Cochrane review concluded that there was no overall benefit at twelve months post-surgery for men who received post-operative PFMT for the treatment of post-prostatectomy urinary incontinence (PPI) and that the benefits of conservative treatment of PPI remain uncertain [168]. A meta-analysis within this review showed that a greater proportion of men were dry from between three and twelve months suggesting that PFMT may speed recovery of continence. A subsequent study adds to this evidence [169].

Two additional RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT [170, 171]. One RCT found that PFMT was helpful in men who had been incontinent for at least one year after prostatectomy, and who had had no previous therapy [172].

One RCT compared PFMT to no treatment in men undergoing TURP. There was no demonstrable difference in the incidence of post-operative incontinence up to twelve months [173].

Summary of evidence	LE
Pelvic floor muscle training (PFMT) for women with urinary incontinence	
Pelvic floor muscle training is better than no treatment for improving urinary incontinence and QoL in women with stress urinary incontinence and mixed urinary incontinence.	1
Higher-intensity, supervised treatment regimes, and the addition of biofeedback, confer greater benefit in women receiving PFMT.	1
Short-term benefits of intensive PFMT are not maintained at fifteen-year follow-up.	2
Pelvic floor muscle training commencing in the early postpartum period improves urinary incontinence in women for up to twelve months.	1

Pelvic floor muscle training for post-prostatectomy urinary incontinence	
Pelvic floor muscle training appears to speed the recovery of continence following radical prostatectomy.	1b
Pelvic floor muscle training does not cure urinary incontinence in men post radical prostatectomy or transurethral prostatectomy.	1b
There is conflicting evidence on whether the addition of bladder training, electrical stimulation or biofeedback increases the effectiveness of PFMT alone.	2
Pre-operative PFMT does not confer additional benefit to men undergoing radical prostatectomy.	1b

For recommendations see section 4.1.3.5.

4.1.3.3.6 Electrical stimulation

The details and methods of delivery of electrical stimulation vary considerably. Electrical stimulation (ES) of the pelvic floor can also be combined with other forms of conservative therapy, e.g. PFMT and biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their pelvic floor muscles. Electrical stimulation is also used in patients with OAB and UUI, for detrusor inhibition. It has been suggested that ES probably targets the pelvic floor directly in SUI and the detrusor muscle or pelvic floor muscle or afferent innervation in UUI.

4.1.3.3.7 Question

In adults with UI, does treatment with ES improve or cure symptoms of UI or QoL compared to no/sham treatment or antimuscarinics?

4.1.3.3.8 Evidence

Most evidence on ES refers to women with SUI. The topic has been included in two HTAs [152, 157] and three systematic reviews [50, 174, 175]. The reviews include analysis of fifteen trials and use different comparison methods, but differ in their assessment of whether ES is more effective than sham stimulation and whether ES adds to the benefit of PFMT alone. Studies were considered to be of generally low quality, with a variety of stimulation parameters, treatment regimens and outcome parameters [168].

A subanalysis in a systematic review on one small low quality RCT in which ES had been compared to oxybutynin and PFMT in patients with UI, showed no difference in incontinence outcomes [176].

A Cochrane review of ES in men with UI (six RCTs) concluded that there was some evidence that electrical stimulation enhanced the effect of PFMT in the short-term but not after six months. Electrical Stimulation was also more effective than sham stimulation at six, but not twelve months. There were, however, more adverse effects (pain or discomfort) with ES [177].

Electromagnetic stimulation has been promoted as treatment for UI but weak evidence of the short-term and long-term effects has been found in systematic reviews [178, 179].

Summary of evidence	LE
In adults with urinary incontinence, electrical stimulation may improve urinary incontinence compared to sham treatment and antimuscarinics.	2
Electrical stimulation may add benefit to pelvic floor muscle training in the short-term.	2

For recommendations see section 4.1.3.5.

4.1.3.4 Posterior tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve (PTNS) delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Stimulation is done percutaneously with a fine, 34-G, needle, inserted just above the medial aspect of the ankle (P-PTNS). Transcutaneous stimulation is also available (T-PTNS). Treatment cycles typically consist of twelve weekly treatments of 30 minutes.

4.1.3.4.1 Question

In adults suffering from UUI, what is the clinical effectiveness of PTNS compared to sham treatment or alternative treatment such as antimuscarinic drugs?

4.1.3.4.2 Evidence

P-PTNS

The reviewed studies included two twelve-week RCTs of PTNS against sham treatment [180, 181], one

comparing PTNS to tolterodine, and a three-year extension trial utilising a maintenance protocol in patients with UUI [182, 183]. The results of studies of PTNS in women with refractory UUI are consistent. Considered together, these results suggest that PTNS improves UUI in women who have had no benefit from antimuscarinic therapy or who are not able to tolerate these drugs. However, there is no evidence that PTNS cures UUI in women. In addition, PTNS is no more effective than tolterodine for improvement of UUI in women. In men there is insufficient evidence to reach a conclusion about efficacy.

T-PTNS

A small RCT compared transcutaneous PTNS plus standard treatment (PFMT and BT) with PFMT and BT alone in older women [184]. Women in the T-TPNS group were more likely to achieve improvement at the end of therapy.

Summary of evidence	LE
Percutaneous posterior tibial nerve stimulation (P-PTNS) appears effective for improvement of urgency urinary incontinence in women who have had no benefit from antimuscarinic medication.	2b
A maintenance programme of P-PTNS has been shown to be effective up to three years.	1b
Percutaneous Posterior tibial nerve stimulation has comparable effectiveness to tolterodine for improvement of urgency urinary incontinence in women.	1b
No serious adverse events have been reported for P-PTNS in urgency urinary incontinence.	3
There is limited evidence for effectiveness of transcutaneous posterior tibial nerve stimulation (PTNS).	2a
There is no evidence that P-PTNS cures urinary incontinence.	2b

4.1.3.5 Recommendations for behavioural and physical therapies

Recommendations	GR
Offer bladder training as a first-line therapy to adults with urgency urinary incontinence or mixed urinary incontinence.	A
Offer prompted voiding for adults with incontinence who are cognitively impaired.	A
Offer supervised intensive pelvic floor muscle training (PFMT), lasting at least three months, as a first-line therapy to women with stress urinary incontinence or mixed urinary incontinence.	A
Pelvic floor muscle training programmes should be as intensive as possible.	B
Offer PFMT to elderly women with urinary incontinence.	A
Offer PFMT to post-natal women with urinary incontinence.	A
Consider using biofeedback as an adjunct in women with stress urinary incontinence.	B
Offer PFMT to men undergoing radical prostatectomy to speed recovery of incontinence.	A
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for the treatment of stress urinary incontinence.	A
Consider offering electrical stimulation as an adjunct to behavioural therapy in patients with urgency urinary incontinence.	B
Do not offer magnetic stimulation for the treatment of incontinence or overactive bladder in adult women.	B
Offer, if available, PTNS as an option for improvement of urgency urinary incontinence in women who have not benefitted from antimuscarinic medication.	B
Support other healthcare professionals in use of rehabilitation programmes including prompted voiding for elderly care-dependent people with urinary incontinence.	A

4.1.4 Conservative therapy in mixed urinary incontinence

About one-third of women with UI have MUI with symptoms of both SUI and UUI, and this becomes more common with increasing age. In terms of evidence base, many studies include patients with MUI, but it is rare for these studies to provide a separate analysis of patients with MUI.

4.1.4.1 Question

In adults with MUI, is the outcome of conservative therapy different to that obtained with the same treatment in patients with either pure SUI or pure UUI?

4.1.4.2 Evidence

No specific systematic reviews were found that addressed the above question. However, a Cochrane report on

pelvic floor muscle training (PFMT) [161] concluded that training was less likely to result in a cure in patients with MUI than in patients with pure SUI, though it is not clear from the report how this conclusion was reached.

A small RCT (n = 71) compared delivery of PFMT, with or without an instructive audiotape. It showed equal efficacy for different types of UI [185].

Following a RCT of PFMT, a review of 88 women available for follow-up at five years found that outcomes were less satisfactory in women with MUI than in women with pure SUI [186].

Summary of evidence	LE
Pelvic floor muscle training appears less effective for mixed urinary incontinence than for stress urinary incontinence alone.	2
Electrical stimulation is equally effective for mixed urinary incontinence and stress urinary incontinence.	1b

4.1.4.3 Recommendations conservative therapy in mixed urinary incontinence

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Warn patients with mixed urinary incontinence that the chance of success of pelvic floor muscle training is lower than for stress urinary incontinence alone.	B

4.2 Pharmacological management

4.2.1 Antimuscarinic drugs

Antimuscarinic (anticholinergic) drugs are currently the mainstay of treatment for UUI. They differ in their pharmacological profiles, e.g. muscarinic receptor affinity and other modes of action, in their pharmacokinetic properties, e.g. lipid solubility and half-life, and in their formulation.

The evaluation of cure or improvement of UI is made harder by the lack of a standard definition of improvement and the failure to use cure as a primary outcome. In general, systematic reviews note that the overall treatment effect of drugs is usually small but larger than placebo.

Dry mouth is the commonest side effect, though constipation, blurred vision, fatigue and cognitive dysfunction may occur [157].

The immediate release (IR) formulation of oxybutynin is the archetype drug in the treatment of UUI. Oxybutynin IR provides maximum dosage flexibility, including an off-label 'on-demand' use. Immediate-release drugs have a greater risk of side effects than extended release (ER) formulations because of differing pharmacokinetics. A transdermal delivery system (TDS) and gel developed for oxybutynin gives a further alternative formulation.

4.2.1.1 Question

In adults with UUI, are antimuscarinic drugs better than placebo for improvement or cure of UUI and for the risk of adverse effects?

4.2.1.2 Evidence

Seven systematic reviews of individual antimuscarinic drugs vs. placebo were reviewed for this section [157, 187-192] as well as studies published since these reviews up until April 2016. Most studies included patients with a mean age of 55-60 years. Both female and male subjects were included in different studies but results cannot be generalised across sexes. Only short-term rates for improvement or cure of UUI are reported. The evidence reviewed was consistent, indicating that ER and IR formulations of antimuscarinics offer clinically significant short-term cure and improvement rates for UUI compared to placebo. On balance, IR formulations tend to be associated with more side effects compared to ER formulations [191].

Cure of UI was deemed to be the most important outcome measure. Risk of adverse events was best represented by withdrawal from a trial because of adverse events, although this does not reflect practice. Table 2 shows a summary of the findings from a systematic review [157]. In summary, every drug where cure of UI was available shows superiority compared to placebo in achieving UI, but the absolute size of effect is small.

Table 2: Summary of cure rates and discontinuation rates of antimuscarinic drugs from RCTs which reported these outcomes [157]

Drug	No. of studies	Patients	Relative risk (95% CI) (of curing UI)	Number needed to treat (95% CI) (to achieve one cure of UI)
Cure of incontinence				
Fesoterodine	2	2,465	1.3 (1.1-1.5)	8 (5-17)
Oxybutynin (includes IR)	4	992	1.7 (1.3-2.1)	9 (6-16)
Propiverine (includes IR)	2	691	1.4 (1.2-1.7)	6 (4-12)
Solifenacin	5	6,304	1.5 (1.4-1.6)	9 (6-17)
Tolterodine (includes IR)	4	3,404	1.2 (1.1-1.4)	12 (8-25)
Trospium (includes IR)	4	2,677	1.7 (1.5-2.0)	9 (7-12)
Discontinuation due to adverse events				
			Relative Risk (95% CI) (of discontinuation)	NNT (95% CI) (of one discontinuation)
Darifenacin	7	3,138	1.2 (0.8-1.8)	
Fesoterodine	4	4,433	2.0 (1.3-3.1)	33 (18-102)
Oxybutynin (includes IR)	5	1,483	1.7 (1.1-2.5)	16 (8-86)
Propiverine (includes IR)	2	1,401	2.6 (1.4-5)	29 (16-77)
Solifenacin	7	9,080	1.3 (1.1-1.7)	78 (39-823)
Tolterodine (includes IR)	10	4,466	1.0 (0.6-1.7)	
Trospium (includes IR)	6	3,936	1.5 (1.1-1.9)	56 (30-228)

4.2.1.2.1 Darifenacin

The cure rates for darifenacin were not included in the AHRQ review. Continence rates were 29-33% for darifenacin compared to 17-18% for placebo [157].

4.2.1.2.2 Transcutaneous oxybutynin

Transdermal oxybutynin has shown a significant improvement in the number of incontinence episodes and micturitions per day vs. placebo and other oral formulations but continence was not reported as an outcome [157].

Oxybutynin topical gel was superior to placebo for improvement of UUI with a higher proportion of participants being cured [157, 193].

There is limited evidence that patients who do not respond to a first-line antimuscarinic treatment may respond to a higher dose or a different antimuscarinic agent [194, 195].

4.2.2 Comparison of antimuscarinic agents

Head-to-head comparison trials of the efficacy and side effects of different antimuscarinic agents are of interest for decision making in practice.

4.2.2.1 Question

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI, and/or a greater improvement in QoL, and/or a lesser likelihood of adverse effects compared to an alternative antimuscarinic drug?

4.2.2.2 Evidence

There are over 40 RCTs and eight systematic reviews [157, 176, 187, 189, 192, 196-198]. Nearly all the primary studies were industry sponsored. Upward dose titration is often included in the protocol for the experimental arm, but not for the comparator arm.

In general, these studies have been designed for regulatory approval. They have short treatment durations (twelve weeks) and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. The clinical utility of these trials in real life practice is questionable. Most trials were of low or moderate quality [189]. The 2012 Agency for Healthcare Research and Quality (AHRQ) review included a specific section addressing comparisons of antimuscarinic drugs (Table 2).

Fesoterodine

Results of an RCT of fesoterodine 4 versus 8 mg suggested a larger therapeutic effect on UUI with the higher dose but with more adverse events [194].

No antimuscarinic agent improved QoL more than another agent [189]. Dry mouth is the most prevalent adverse effect. Good evidence indicates that, in general, higher doses of any drug are likely to be associated with higher rates of adverse events. Also, ER formulations of short-acting drugs and longer-acting drugs are generally associated with lower rates of dry mouth than IR preparations [189, 196]. Oxybutynin IR showed higher rates of dry mouth than tolterodine IR and trospium IR, but lower rates of dry mouth than darifenacin, 15 mg daily [189, 196]. Overall, oxybutynin ER has higher rates of dry mouth than tolterodine ER, although the incidence of moderate or severe dry mouth were similar. Transdermal oxybutynin had a lower rate of dry mouth than oxybutynin IR and tolterodine ER, but had an overall higher rate of withdrawal due to an adverse skin reaction [189]. Solifenacin, 10 mg daily, had higher rates of dry mouth than tolterodine ER [189]. Fesoterodine, 8 mg daily, had a higher rate of dry mouth than tolterodine, 4 mg daily [199-201]. In general, similar discontinuation rates were observed, irrespective of differences in the occurrence of dry mouth (doses have been given were the evidence relates to a specific dose level typically from trials with a dose escalation element).

Summary of evidence	LE
There is limited evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of urgency urinary incontinence.	1b
Higher doses of antimuscarinic drugs are more effective to cure or improve urgency urinary incontinence, but with a higher risk of side effects.	1b
Once daily (extended release) formulations are associated with lower rates of adverse events compared to immediate release ones, although similar discontinuation rates are reported in clinical trials.	1b
Dose escalation of antimuscarinic drugs may be appropriate in selected patients to improve treatment effect although higher rates of adverse events can be expected.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral antimuscarinic drugs, but has a high rate of withdrawal due to skin reaction.	1b

4.2.3 **Antimuscarinic drugs vs. conservative treatment**

The choice of drug vs. conservative treatment of UUI is an important question.

4.2.3.1 *Question*

In adults with UUI, does one type of antimuscarinic drug result in a greater likelihood of cure or improvement in UUI and/or greater improvement in QoL, and/or lesser likelihood of adverse effects compared to conservative treatment?

4.2.3.2 *Evidence*

More than 100 RCTs and high-quality reviews are available [158, 176, 189, 190, 202, 203]. Most of these studies were independent. A US HTA [176] found that trials were of a low- or moderate-quality. The main focus of the review was to compare the different drugs used to treat UUI. In one study, multicomponent behavioural modification produced significantly greater reductions in incontinence episodes compared to oxybutynin and higher patient satisfaction for behavioural vs. drug treatment. In men with storage LUTS no difference in efficacy was found between oxybutynin and behavioural therapy [204].

The combination of BT and solifenacin in women with OAB conferred no additional benefit in terms of continence [205]. A recent Cochrane review on the benefit of adding PFMT to other active treatments of UI in women showed insufficient evidence of any benefit in adding PFMT to drug treatment [206].

One RCT [207] reported a similar improvement in subjective parameters with either transcutaneous electrical nerve stimulation (T-PTNS) or oxybutynin. One study compared tolterodine ER to transvaginal/anal electrical stimulation without differences in UI outcomes [208].

Summary of evidence	LE
There is no consistent evidence to show superiority of drug therapy over conservative therapy for treatment of urgency urinary incontinence.	1b
Behavioural treatment has higher patient satisfaction than drug treatment.	1b
There is insufficient evidence as to the benefit of adding pelvic floor muscle training to drug treatment for urgency urinary incontinence.	1b

4.2.3.3 Recommendations for antimuscarinic drugs

Recommendations	GR
Offer antimuscarinic drugs for adults with urgency urinary incontinence who failed conservative treatment.	A
Consider extended release formulations in patients who do not tolerate immediate release antimuscarinics.	A
If antimuscarinic treatment proves ineffective, consider dose escalation or offering an alternative treatment.	B
Consider using transdermal oxybutynin if oral antimuscarinic agents cannot be tolerated due to dry mouth.	B
Offer and encourage early review (of efficacy and side effects) of patients on antimuscarinic medication for urgency urinary incontinence.	C

4.2.4 Antimuscarinic agents: adherence and persistence

Most studies on antimuscarinic medication are short term (twelve weeks). Adherence in clinical trials is considered to be much higher than in clinical practice [209].

4.2.4.1 Question

Do patients with UUI adhere to antimuscarinic drug treatment and persist with prescribed treatment in clinical practice?

4.2.4.2 Evidence

This topic has been reviewed for the development of these Guidelines [210]. Two open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at two years of 49-84% [211, 212]. The main drugs studied were oxybutynin and tolterodine IR and ER. Non-persistence rates were high for tolterodine at twelve months, and particularly high (68-95%) for oxybutynin.

Five articles reported 'median days to discontinuation' as between < 30 days and 50 days [213-217]. In a military health system where free medication was provided, the median time to discontinuation extended to 273 days [214].

Data on adherence/persistence from open-label extension populations are questionable as these patients are self-selected to be compliant. A Longitudinal Disease Analyser database study has indicated an increasing discontinuation rate from 74.8% at one year to 87% at three years [218].

Several of the RCT trials tried to identify the factors associated with low/lower, adherence or persistence of antimuscarinics. These were identified as:

- low level of efficacy (41.3%);
- adverse events (22.4%);
- cost (18.7%), higher adherence rates were observed when drugs were provided at no cost to the patient [214].

Other reasons for poor adherence included:

- IR vs. ER formulations;
- age (lower persistence among younger adults);
- unrealistic expectations of treatment;
- gender distribution (better adherence/persistence in female patients);
- ethnic group (African-Americans and other ethnic minorities are more likely to discontinue or switch treatment).

In addition, the data source influenced the adherence figures.

Summary of evidence	LE
Adherence to antimuscarinic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost.	2
Most patients will stop antimuscarinic agents within the first three months.	2

4.2.5 **Antimuscarinic and beta3 agonist agents, the elderly and cognition**

Trials have been conducted in elderly people with UI. Considerations in this patient group include the multifactorial aetiology of UI in the elderly, comorbidities such as cognitive impairment, the effect of co-medications and the risk of adverse events.

The effects of antimuscarinic agents on cognition have been studied in more detail.

4.2.5.1 *Question*

What is the comparative efficacy, and risk of adverse effects, particularly the cognitive impact, of treatment with antimuscarinic medication in elderly men and women with UUI?

4.2.5.2 *Evidence*

Two systematic reviews focusing on elderly patients are available [219, 220]. A community-based cohort study found a high incidence of cognitive dysfunction [221]. Other systematic reviews have included sections on the efficacy and safety of antimuscarinics in elderly patients [157, 189]. A systematic review in 2012 found inconclusive evidence as to the impact of antimuscarinics on cognition [222].

Two recent longitudinal cohort studies in patients using drugs with antimuscarinic effect showed a deterioration in cognitive function, alteration in CNS metabolism and an association with brain atrophy [223, 224]. In general, the long-term impact of antimuscarinic agents specifically approved for OAB treatment on specific patient cohorts is poorly understood [225-228].

4.2.5.2.1 *Oxybutynin*

There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults [225, 227, 229-233]. Recent evidence has emerged from a prospective cohort study showing cumulative cognitive deterioration associated with prolonged use of antimuscarinic medication including oxybutynin [223].

More rapid functional deterioration might result from the combined use of cholinesterase inhibitors with antimuscarinic agents in elderly patients with cognitive dysfunction [234].

4.2.5.2.2 *Solifenacin*

One pooled analysis [235] has shown that solifenacin does not increase cognitive impairment in the elderly. No age-related differences in the pharmacokinetics of solifenacin in different age groups was found, although more frequent adverse events in subjects over 80 years of age were observed. No cognitive effect on healthy elderly volunteers was shown [233]. In a subanalysis of a large trial, solifenacin 5-10 mg improved symptoms and QoL in people ≥ 75 years who had not responded to tolterodine [236]. In patients with mild cognitive impairment, ≥ 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most side effects compared to oxybutynin IR [232, 237].

4.2.5.2.3 *Tolterodine*

No change in efficacy or side effects related to age have been reported, although a higher discontinuation rate was found for both tolterodine and placebo in elderly patients [225]. Two RCTs in the elderly found a similar efficacy and side effect profile to younger patients [238-241]. Post-hoc analysis has shown little effect on cognition. One non-randomised comparison showed lower rates of depression in elderly participants treated with tolterodine ER compared to oxybutynin IR [242].

4.2.5.2.4 *Darifenacin*

Two RCTs in the elderly population (one in patients with UUI and the other in volunteers) concluded that darifenacin was effective with no risk of cognitive change, measured as memory scanning tests, compared to placebo [243, 244]. Another study on darifenacin and oxybutynin ER in elderly subjects concluded that the two agents had a similar efficacy, but that cognitive function was more often affected in the oxybutynin ER arm [227].

4.2.5.2.5 Trosipium chloride

Trosipium does not appear to cross the blood brain barrier in significant amounts in healthy individuals due to its molecular characteristics (quaternary amine structure and hydrophilic properties). Two (EEG) studies in healthy volunteers showed no effect from trosipium whilst tolterodine caused occasional changes and oxybutynin caused consistent changes [245, 246]. No evidence as to the comparative efficacy and side effect profiles of trosipium in different age groups is available. However, there is some evidence that trosipium does not impair cognitive function [228, 247] and that it is effective compared to placebo in the elderly [248].

4.2.5.2.6 Fesoterodine

Pooled analyses of the RCTs of fesoterodine confirmed the efficacy of the 8 mg but not the 4 mg dose in over-75-year olds [211]. Adherence was lower in the over-75 year-old group but the effect on mental status was not reported [201, 211, 249]. A more recent RCT showed efficacy of fesoterodine in the vulnerable elderly with no differences in cognitive function at twelve weeks [250].

4.2.5.2.7 Duloxetine in the elderly

RCTs comparing duloxetine and placebo included women up to 85 years, but no age stratification of the results is available [190, 251, 252].

4.2.5.2.8 Mirabegron

Analysis of pooled data from three RCTs showed efficacy and safety of mirabegron in elderly patients [253].

4.2.5.2.9 Applicability of evidence to general elderly population

It is not clear how much the data from pooled analyses and subgroup analyses from large RCTs can be extrapolated to a general ageing population. Community-based studies of the prevalence of antimuscarinic side effects may be the most helpful [221]. When starting anticholinergics in elderly patients, mental function should be assessed objectively and monitored [254]. No consensus exists as to the best mental function test to detect changes in cognition [234, 255].

4.2.5.2.10 Anticholinergic load

A number of medications have anticholinergic effects and their cumulative effects on cognition should be considered [256].

4.2.5.2.11 Question

In older people suffering from UI, what is the effect of anticholinergic burden (defined by anticholinergic cognitive burden scale) on cognitive function?

4.2.5.2.12 Evidence

No studies were identified specifically in older people with UI, but evidence was available from observational cohort studies relating to the risk in a general population of older people. Lists of drugs with anticholinergic properties are available from two sources [256, 257].

Two systematic reviews of largely retrospective cohort studies showed a consistent association between long-term anticholinergic use and cognitive dysfunction [258, 259].

Longitudinal studies in older people over two to four years have found increased rate of decline in cognitive function for patients on anticholinergics or drugs with anticholinergic effects [223, 224, 260, 261].

Summary of evidence	LE
Antimuscarinic drugs are effective in elderly patients.	1b
Mirabegron has been shown to be efficacious and safe in elderly patients.	1b
In older people, the cognitive impact of drugs which have anticholinergic effects is cumulative and increases with length of exposure.	2
Oxybutynin may worsen cognitive function in elderly patients.	2
Solifenacin, darifenacin, fesoterodine and trosipium have been shown not to cause cognitive dysfunction in elderly people in short-term studies.	1b

4.2.5.2.13 Additional recommendations for antimuscarinic drugs in the elderly

Recommendations	GR
In older people being treated for urinary incontinence, every effort should be made to employ nonpharmacological treatments first.	C
Long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction.	B*
When prescribing antimuscarinic for urgency urinary incontinence, consider the total antimuscarinic load in older people on multiple drugs.	C
Consider the use of mirabegron in elderly patients if additional antimuscarinic load is to be avoided.	C

*Recommendation based on expert opinion.

4.2.5.3 Research priorities

- All drug trials should report cure rates for urinary incontinence based on a bladder diary.
- What is the relative incidence of cognitive side effects of antimuscarinic drugs?

4.2.6 **Mirabegron**

Mirabegron is the first clinically available beta3 agonist, available from 2013. Beta3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation.

Mirabegron has undergone evaluation in industry-sponsored phase 2 and phase 3 trials [262-265]. Three systematic reviews assessing the clinical effectiveness of mirabegron [262, 263, 266] reported that mirabegron at doses of 25, 50 and 100 mg, results in significantly greater reduction in incontinence episodes, urgency episodes and micturition frequency/24 hours than placebo, with no difference in the rate of common adverse events [262]. The placebo dry rates in most of these trials are between 35-40%, and 43 and 50% for mirabegron. In all trials the statistically significant difference is consistent only for improvement but not for cure of UI. Similar improvement in frequency of incontinence episodes and micturitions/24 hours was found in people who had previously tried and those who had not previously tried antimuscarinic agents. One systematic review showed that mirabegron is similarly efficacious as most antimuscarinics in reducing UUI episodes [267].

The most common treatment adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%), with the overall rate similar to placebo [262, 265, 268].

In a twelve-month, active-controlled RCT of mirabegron 50/100 mg vs. tolterodine ER 4 mg, the improvement in efficacy seen at twelve weeks was sustained at twelve-month evaluation in all groups. The reported dry rates at twelve months were 43%, 45% and 45% for mirabegron 50 mg, 100 mg and tolterodine 4 mg respectively [268]. Post hoc analyses of RCTs showed that clinical improvement observed in parameters of OAB severity translates to an improvement in HRQoL and efficacy is maintained in patients with more severe degree of UI [269, 270].

No risk of QTc prolongation on electrocardiogram [271] and raised intraocular pressure [272] were observed up to 100 mg dose; however, patients with uncontrolled hypertension or cardiac arrhythmia were excluded from these trials. There is no significant difference in rate of side effects at different doses of mirabegron [268]. Data from a large Canadian Private Drug Plan database suggest a higher adherence rate for mirabegron compared to antimuscarinics [273]. Patients on certain concurrent medications (i.e. metoprolol) should be counselled that, due to common metabolism pathways, their medication dosage may need to be adjusted. In the case of patients taking metoprolol, blood pressure should be monitored after starting mirabegron and, if necessary, metoprolol dosing changed.

Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron (50 or 100 mg) did not adversely affect voiding urodynamic parameters compared to placebo [274].

Equivalent adherence was observed for tolterodine and mirabegron at twelve months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [268]. In mirabegron treated patients, improvement in objective outcome measures correlates directly with clinically relevant PROMs (OAB-q and PPBC) [269, 275].

An RCT in patients who had inadequate response to solifenacin monotherapy 5 mg, demonstrated that

combination treatment with mirabegron 50 mg had a higher chance of achieving clinically meaningful improvement in UI as compared to dose escalation of solifenacin [276].

Summary of evidence	LE
Mirabegron is better than placebo and as efficacious as antimuscarinics for improvement of urgency urinary incontinence symptoms.	1a
Adverse event rates with mirabegron are similar to placebo.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron than dose escalation of solifenacin.	1b

Recommendation	GR
In patients with UUI and an inadequate response to conservative treatments offer mirabegron, unless they have uncontrolled hypertension.	A

4.2.7 **Drugs for stress urinary incontinence**

Duloxetine inhibits the presynaptic re-uptake of neurotransmitters, serotonin (5-HT) and norepinephrine (NE). In the sacral spinal cord, an increased concentration of 5-HT and NE in the synaptic cleft increases stimulation of 5-HT and NE receptors on the pudendal motor neurones, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

4.2.7.1 *Questions*

- In adults with SUI, does duloxetine cure or improve UI and/or improve QoL compared to no treatment?
- In adults with SUI, does duloxetine result in a greater cure or improvement of UI, or a greater improvement in QoL, or a lesser likelihood of adverse effects, compared to any other intervention?

4.2.7.2 *Evidence*

Duloxetine was evaluated as a treatment for female SUI or MUI in three systematic reviews [190, 251, 252].

Improvement in UI compared to placebo was observed with no clear differences between SUI and MUI. One study reported cure for UI in about 10% of patients. An improvement in I-QoL was not found in the study using I-QoL as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [277], duloxetine reduced leakage compared to PFMT or no treatment. Global improvement and QoL were better for combined therapy than no treatment. There was no significant difference between PFMT and no treatment.

Two open-label studies with a follow-up of one year or more evaluated the long-term effect of duloxetine in controlling SUI; however, both had high discontinuation rates [278, 279].

All studies had a high patient withdrawal rate, which was caused by a lack of efficacy and high incidence of adverse events, including nausea and vomiting (40% or more of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue, amongst other causes [278, 279].

A systematic review showed significant efficacy for duloxetine compared to placebo in women with UI but with increased risk of adverse events [252].

Summary of evidence	LE
Duloxetine, 40 mg twice daily improves stress urinary incontinence in women.	1a
Duloxetine causes significant gastrointestinal and central nervous system side effects leading to a high rate of treatment discontinuation, although these symptoms are limited to the first weeks of treatment.	1a

Recommendations	GR
Duloxetine can be used with caution to treat women with symptoms of stress urinary incontinence.	A
Duloxetine should be initiated using dose titration because of high adverse event rates.	A

4.2.8 **Oestrogen**

Oestrogenic drugs including conjugated equine oestrogens, oestradiol, tibolone and raloxifene, are used as hormone replacement therapy (HRT) for women with natural or therapeutic menopause.

Oestrogen treatment for UI has been tested using oral, transdermal and vaginal routes of administration. Available evidence suggests that vaginal oestrogen treatment with oestradiol and oestriol is not associated with the increased risk of thromboembolism, endometrial hypertrophy, and breast cancer seen with systemic administration [280-282]. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women.

4.2.8.1 Questions

- In women with UI, does vaginal (local) oestrogen cure or improve UI compared to no treatment or other active treatment?
- In women with UI, does oral (systemic) oestrogen cure or improve UI compared to no treatment?

4.2.8.2 Evidence

Vaginal oestrogens

A Cochrane systematic review looked at the use of oestrogen therapy in postmenopausal women [280] given local oestrogen therapy. There is also a more recent narrative review of oestrogen therapy in urogenital diseases [283]. The Cochrane review (search date cut off June 2012) found that vaginal oestrogen treatment improved symptoms of UI in the short term [280]. The review found small, low quality trials comparing vaginal oestrogen treatment with phenylpropanolamine, PFMT, electrical stimulation and its use as an adjunct to surgery for SUI. Local oestrogen was less likely to improve UI than PFMT but no differences in UI outcomes were observed for the other comparisons. A single trial of local oestrogen therapy comparing a ring device to pessaries found no difference in UI outcomes although more women preferred the ring device. No adverse effects of vaginal administration of oestradiol for vulvovaginal atrophy over two years was seen in one trial [284].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. The ideal treatment duration and the long-term effects are uncertain. A standardised review of local oestrogen showed improvement of UI over placebo with vaginal rings favoured subjectively over pessaries; no significant difference between vaginal and oral oestrogen treatments was found [285].

One RCT in postmenopausal women showed benefit in adding intravaginal oestriol to vaginal ES and PFMT [286].

Systemic oestrogens

Studies of HRT with non-urogenital primary outcomes have looked for change in urinary continence in secondary analyses. Large trials using conjugated equine oestrogens showed a higher rate of development or worsening of UI compared to placebo [287-290]. In a single RCT, use of raloxifene was not associated with development or worsening of UI [291]. Three small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [50, 292, 293].

Summary of evidence	LE
Vaginal oestrogen therapy improves urinary incontinence for post-menopausal women in the short term.	1a
Neoadjuvant or adjuvant use of local oestrogens are ineffective as an adjunct to surgery for urinary incontinence.	2
Systemic hormone replacement therapy using conjugate equine oestrogens in previously continent women increases the risk of developing urinary incontinence and worsens pre-existing urinary incontinence.	1a

Recommendations	GR
Offer post-menopausal women with urinary incontinence vaginal oestrogen therapy, particularly if other symptoms of vulvovaginal atrophy are present.	A
Vaginal oestrogen therapy for vulvovaginal atrophy should be prescribed long-term. In women with a history of breast cancer, the treating oncologist needs to be consulted.	C
For women taking oral conjugated equine oestrogen as hormone replacement therapy who develop or experience worsening urinary incontinence, discuss alternative hormone replacement therapies.	A
Advise women who are taking systemic oestradiol who suffer from urinary incontinence that stopping the oestradiol is unlikely to improve their incontinence.	A

4.2.9 **Desmopressin**

Desmopressin is a synthetic analogue of vasopressin (also known as antidiuretic hormone). It can be taken orally, nasally or by injection. Desmopressin is most commonly used to treat diabetes insipidus and, when used at night, to treat nocturnal enuresis.

4.2.9.1 *Questions*

- In adults with UI, does desmopressin cure or improve UI and/or improve QoL compared to no treatment?
- In adults with UI, does desmopressin result in a lesser likelihood of adverse effects, compared to any other intervention?

4.2.9.2 *Evidence*

4.2.9.2.1 Improvement of incontinence

Few studies have examined the use of desmopressin exclusively for the treatment of UI. No evidence was found that demonstrated any effect of desmopressin on nocturnal incontinence, though evidence does exist for it reducing nocturnal polyuria, particularly in children [294]. One RCT compared desmopressin to placebo with daytime UI as an outcome measure, with improved continence shown during the first four hours after taking desmopressin in women [295]. There is no evidence reporting desmopressin cure rates for UI and no evidence that compares desmopressin with other non-drug treatments for UI.

4.2.9.2.2 Monitoring for hyponatraemia

The use of desmopressin carries a risk of developing hyponatraemia (please refer to the EAU Guidelines on Male LUTS [27]).

Summary of evidence	LE
The risk of urinary incontinence is reduced within four hours of taking oral desmopressin, but not after four hours.	1b
Continuous use of desmopressin does not improve or cure urinary incontinence.	1b
Regular use of desmopressin may lead to hyponatraemia.	3

Recommendations	GR
Consider offering desmopressin to patients requiring occasional short-term relief from daytime urinary incontinence and inform them that this drug is not licensed for this indication.	A
Monitor plasma sodium levels in patients on desmopressin.	A*
Do not use desmopressin for long-term control of urinary incontinence.	A

*Recommendation based on expert opinion.

4.2.10 **Drug treatment in mixed urinary incontinence**

4.2.10.1 *Question*

In adults with MUI, is the outcome of a drug treatment different to that for the same treatment in patients with either pure SUI or UUI?

4.2.10.2 *Evidence*

Many RCTs include patients with MUI with predominant symptoms of either SUI or UUI but few report outcomes separately for those with MUI compared to pure SUI or UUI groups.

Tolterodine

In an RCT of 854 women with MUI, tolterodine ER was effective for improvement of UUI, but not SUI suggesting that the efficacy of tolterodine for UUI was not altered by the presence of SUI [296]. In another study (n = 1380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [297]. Similar results were found for solifenacin [298, 299].

Duloxetine

In one RCT of duloxetine vs. placebo in 588 women, subjects were stratified into either stress-predominant, urgency-predominant or balanced MUI groups. Duloxetine was effective for improvement of incontinence and QoL in all subgroups [300].

Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of respective subpopulations [301].

Summary of evidence	LE
Limited evidence suggests that antimuscarinic drugs are effective for improvement of the urgency urinary incontinence component in patients with mixed urinary incontinence.	2
Duloxetine is effective for improvement of both stress urinary incontinence and urgency urinary incontinence in patients with mixed urinary incontinence.	1b

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Offer antimuscarinic drugs or beta3 agonists to patients with urgency-predominant mixed urinary incontinence.	A*
Consider duloxetine for patients with mixed urinary incontinence unresponsive to other conservative treatments and who are not seeking cure.	B

*Recommendation based on expert opinion.

4.3 Surgical management

In line with the recommendations from the UK National Institute for Healthcare and Clinical Excellence (NICE) [50] the Panel agreed that surgeons and centres performing surgery should:

- be properly trained in each procedure;
- not be trained by someone who is not surgically qualified;
- perform sufficient numbers of a procedure to maintain expertise of him/herself and the surgical team;
- be able to offer alternative surgical treatments;
- be able to deal with the complications of surgery;
- provide suitable arrangements for follow-up, long-term if necessary.

This section considers surgical options for the following situations:

- Women with uncomplicated SUI: This means no history of previous surgery, no neurogenic LUT dysfunction, no bothersome genitourinary prolapse, and women not considering further pregnancy.
- Women with complicated SUI: Neurogenic LUT dysfunction is reviewed in the EAU Guidelines on Neuro-Urology [2].
- Associated genitourinary prolapse has been included in these Guidelines in terms of treating incontinence, but no attempt has been made to comment on treatment of prolapse itself.
- Men with SUI: mainly men with post-prostatectomy incontinence without neurological disease affecting the lower urinary tract.
- Patients with refractory DO incontinence.

Although the outcome of surgical procedures should be considered in absolute terms, it is also important to consider any associated complications, adverse events and costs. The outcome parameters used to evaluate surgery for SUI have included:

- continence rate and number of incontinence episodes;
- general and procedure-specific complications;
- generic, specific (UI) and correlated (sexual and bowel) QoL.

The Panel has tried to acknowledge emerging techniques as they considered appropriate and have made a strong recommendation (section 4.3.1.5.2) that new devices are only used as part of a structured research programme.

4.3.1 Women with uncomplicated stress urinary incontinence

4.3.1.1 Mid-urethral slings

Early clinical studies identified that slings should be made from monofilament, non-absorbable material, typically polypropylene, and constructed as a 1-2 cm wide mesh with a relatively large pore size (macroporous). Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.

4.3.1.1.1 Questions

In women with SUI, what is the effectiveness in curing SUI and adverse effects at one year for:

- mid-urethral synthetic sling insertion compared to Burch colposuspension?
- one method of insertion of a mid-urethral synthetic sling compared to another method?
- one direction of insertion of a mid-urethral synthetic sling compared to another direction of insertion?

4.3.1.1.2 Evidence

For the purpose of these Guidelines, a new meta-analysis was performed.

Mid-urethral sling insertion compared to colposuspension

Thirteen RCTs (n = 1037) compared mid-urethral sling (retropubic) and colposuspension (open and laparoscopic). The meta-analysis found no difference in patient-reported cure rates at twelve months [302-312]. The overall patient-reported cure rate was 75%. There was weak evidence of higher clinician-reported cure rates at twelve months after mid-urethral sling (83%) compared to colposuspension (78%) [305-312]. Longer-term follow-up for up to five years reported no difference in effectiveness, though the numbers of participants lost to follow-up was high [76, 304]. Voiding dysfunction was more likely for colposuspension (relative risk 0.34, 95% CI 0.16-0.7) whilst bladder perforation was higher for the mid-urethral sling (15% vs. 9%, and 7% vs. 2%, respectively) [303, 305, 313-315].

Transobturator route vs. retropubic route

The EAU Panel meta-analysis identified 34 RCTs (5,786 women) comparing insertion of the mid-urethral sling by the retropubic and transobturator routes. There was no difference in cure rates at twelve months in either patient-reported or clinically reported cure rates (77% and 85%, respectively) [5]. Voiding dysfunction was less common (4%) following transobturator insertion compared to retropubic insertion (7%), as was the risk of bladder perforation (0.3%) or urethral perforation (5%). The risks of *de novo* urgency and vaginal perforation were 6% and 1.7%, respectively. Chronic perineal or groin/thigh pain at twelve months after surgery was reported by 21 trials and meta-analysis showed a higher rate in women undergoing transobturator insertion (7%) compared to retropubic insertion (3%).

Insertion using a skin-to-vagina direction vs. a vagina-to-skin direction

A Cochrane systematic review and meta-analysis found that the skin-to-vagina direction (top - down) for retropubic insertion of mid-urethral slings was less effective than the vagina-to-skin (bottom - up) direction and was associated with higher rates of voiding dysfunction, bladder perforation and vaginal erosion [316]. A further systematic review and meta-analysis found that the skin-to-vagina (outside in) direction of transobturator insertion of mid-urethral slings was equally effective compared to the vagina-to-skin route (inside out) using direct comparison. However, indirect comparative analysis gave weak evidence for a higher rate of voiding dysfunction and bladder injury [317].

4.3.1.2 Adjustability

4.3.1.2.1 Questions

- In women with SUI, does an adjustable sling cure SUI and improve QoL or does it cause adverse outcome(s)?
- How does an adjustable sling compare to other surgical treatments for SUI?

4.3.1.2.2 Evidence

There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There are limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definitions. Few studies include sufficient numbers of patients or have a long enough follow-up to provide useful evidence. The available devices have differing designs, making it difficult to draw general conclusions about adjustable slings as a class of procedure.

4.3.1.3 Single-incision slings

4.3.1.3.1 Questions

- In women with SUI, do single-incision slings cure UI or improve QoL, or cause adverse outcomes?
- How does a single-incision sling compare to other surgical treatments for SUI?

4.3.1.3.2 Evidence

Although there have been many studies published on single-incision devices, it should be noted that there are significant differences in technical design between devices and it may be misleading to make general statements about them as a class of operations. It should also be noted that some devices have been withdrawn from the market (e.g. TVT Secur[®], Minitape), and yet evidence relating to these may be included in current meta-analyses. There was evidence to suggest single-incision slings are quicker to perform and cause less post-operative thigh pain, but there was no difference in the rate of chronic pain. There was not enough evidence to conclude any difference between single-incision slings in direct comparisons.

The most recent meta-analysis [318] and a re-analysis of the Cochrane review data by the Panel (excluding TVT Secur[®] data) have demonstrated that there was no difference in efficacy between available single-incision devices and conventional mid-urethral slings. However, not all single-incision devices have been subjected to RCT evaluation and it may be unsafe to assume that they are collectively technically similar devices.

Generalisability of evidence to adult women with SUI

Analysis of the population studied in trials included in this meta-analysis suggests that the evidence is generalisable to women who have predominantly SUI, and no other clinically severe lower genitourinary tract dysfunction. The evidence is not adequate to guide choice of surgical treatment for those women with MUI, severe POP, or a history of previous surgery for SUI. The results of the EAU Panel meta-analysis [5] were consistent with those of the Cochrane systematic review [316], except that in the EAU Panel meta-analysis the objective cure rates appeared slightly higher for retropubic (88%) compared to transobturator insertion (84%). The EAU Panel finding is consistent with an additional systematic review and meta-analysis [319] and the difference may result from the Panel's decision to only consider trial data with at least twelve months of follow-up.

Sexual function after mid-urethral tape surgery

A systematic review concluded there was a lack of RCTs addressing the effects of incontinence surgery on sexual function but noting a reduction in coital incontinence [320]. One RCT [321] and another cohort study [322] have shown that overall sexual activity improves after sling surgery.

SUI surgery in the elderly

There are no RCTs comparing surgical treatment in older vs. younger women, although subgroup analyses of some RCTs have included a comparison of older with younger cohorts. Definitions of elderly vary from one study to another so no attempt was made to define the term here. Instead, the Panel attempted to identify those studies which have addressed age difference as an important variable.

A RCT of 537 women comparing retropubic to transobturator tape, showed that increasing age was an independent risk factor for failure of surgery over the age of 50 [323]. An RCT assessing risk factors for the failure of TVT vs. transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at one year [324]. In a subanalysis of a trial cohort of 655 women at 2 years' follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI 1.7-7.97), are less likely to report objective or subjective improvement in stress and urgency UI, and are more likely to undergo retreatment for SUI (OR 3.9, 95% CI 1.3-11.48). There was no difference in time to post-operative normal voiding [325].

Another RCT comparing immediate TVT vs. no surgery (delayed TVT) in older women, confirmed efficacy of surgery in terms of QOL and satisfaction, but with higher complication rates [326].

A cohort study of 256 women undergoing inside-out transobturator tape reported similar efficacy in older vs. younger women, but found a higher risk of *de novo* urgency in older patients [327].

Summary of evidence	LE
Compared to colposuspension, the retropubic insertion of a mid-urethral synthetic sling provides equivalent patient-reported cure of stress urinary incontinence at five years.	1a
Mid-urethral synthetic sling inserted by either the transobturator or retropubic route provides equivalent patient-reported outcome at twelve months.	1a
Mid-urethral sling insertion is associated with a lower rate of a new symptom of urgency, and voiding dysfunction, compared to colposuspension.	1a
The retropubic route of insertion is associated with a higher intra-operative risk of bladder perforation and a higher rate of voiding dysfunction than the transobturator route.	1a
The transobturator route of insertion is associated with a higher risk of chronic pain and vaginal erosion and extrusion at twelve months, than that found with the retropubic route.	1a
The skin-to-vagina direction of both retropubic and transobturator insertion is associated with a higher risk of post-operative voiding dysfunction.	1b
Adjustable mid-urethral synthetic sling devices may be effective for cure or improvement of stress urinary incontinence in women.	3
There is no evidence that adjustable slings are superior to standard mid-urethral slings.	4
The comparative efficacy of single-incision slings against conventional mid-urethral slings is uncertain.	1b

Operation times for insertion of single-incision mid-urethral slings are shorter than for standard retropubic slings.	1b
Blood loss and immediate post-operative pain are lower for insertion of single-incision slings compared with conventional mid-urethral slings.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with conventional mid-urethral slings.	1b
Older women benefit from surgical treatment for urinary incontinence.	1
The risk of failure from surgical repair of stress urinary incontinence, or suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4
In women undergoing surgery for stress urinary incontinence, coital incontinence is likely to improve.	3
Overall, sexual function is unlikely to deteriorate following stress urinary incontinence surgery.	3
There is no consistent evidence that the risk of post-operative sexual dysfunction differs between midurethral sling procedures.	3

NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure (TVTS) device and although this device is no longer available, many women still have the device in place.

4.3.1.4 Open and laparoscopic surgery for stress urinary incontinence

Open colposuspension was previously considered the most appropriate surgical intervention for SUI, and was used as the comparator in RCTs of newer, less invasive, surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally invasive approach.

4.3.1.4.1 Question

In women with SUI, what is the effectiveness of open and laparoscopic surgery, compared to other surgical procedures, measured in terms of cure or improvement of incontinence or QoL, or the risk of adverse events?

4.3.1.4.2 Evidence

Four systematic reviews were found, which covered the subject of open surgery for SUI, including 46 RCTs [2, 328-330], but no RCTs comparing any operation to a sham procedure were identified.

Open colposuspension

The Cochrane review [330] included 46 trials in which 4,738 women had open colposuspension. In most of these trials, open colposuspension was used as the comparator to an experimental procedure. Consequently, for this review we have only considered the absolute effect of colposuspension, but have not reviewed all of these comparisons. No additional trials have been reported since this review.

Within the first year, complete continence rates of approximately 85-90% were achieved for open colposuspension, while failure rates for UI were 17% up to five years and 21% over five years. The re-operation rate for UI was 2%. Colposuspension was associated with a higher rate of development, at five years, of enterocele/vault/cervical prolapse (42%) and rectocele (49%) compared to tension-free vaginal tape (TVT) (23% and 32%, respectively). The rate of cystocele was similar in colposuspension (37%) and with TVT (41%).

Four trials compared Burch colposuspension to the Marshall Marchetti Krantz procedure and one trial evaluated Burch colposuspension with paravaginal repair. All showed fewer surgical failures up to five years with colposuspension but otherwise reported similar outcomes.

Anterior colporrhaphy

Anterior colporrhaphy is now considered an obsolete operation for UI. In a Cochrane review [329], ten trials compared anterior colporrhaphy (n = 385) with colposuspension (n = 627). The failure rate for UI at follow-up of up to five years was worse for anterior colporrhaphy with a higher requirement for re-operation for incontinence.

Autologous fascial sling

The Cochrane review [329, 331] described 26 RCTs, including 2,284 women undergoing autologous sling procedure in comparison to other operations.

There were seven trials of autologous fascial sling vs. colposuspension. Except for one very high-quality study [49] showing superiority of fascial sling most of the studies were of variable quality, with a few very small studies and short follow-up. The meta-analysis showed that fascial sling and colposuspension had a similar cure rate at one year. Colposuspension had a lower risk of voiding difficulty and UTIs, but a higher risk of bladder perforation.

In twelve trials of autologous fascial sling vs. mid-urethral synthetic slings, the procedures showed similar efficacy. However, use of the synthetic sling resulted in shorter operating times and lower rates of complications, including voiding difficulty. Six trials compared autologous fascial slings with other materials of different origins, with results favouring traditional autologous fascial slings. Post-hoc analysis of an RCT comparing the autologous fascial sling to Burch colposuspension showed inferior outcomes for women who suffered pre-operative urgency [325].

Laparoscopic colposuspension

The Cochrane review [328] identified 22 RCTs, of which ten trials compared laparoscopic colposuspension to open colposuspension. No other trials have been identified. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were less good for laparoscopic colposuspension. However, laparoscopic colposuspension had a lower risk of complications and shorter duration of hospital stay.

In eight RCTs comparing laparoscopic colposuspension to mid-urethral slings, the subjective cure rates were similar, while the objective cure rate favoured the mid-urethral sling at eighteen months. Complication rates were similar for the two procedures and operating times were shorter for the mid-urethral sling. Comparisons of colposuspension to mid-urethral sling are covered in section 4.3.1.1.

Summary of evidence	LE
Autologous fascial sling is more effective than colposuspension for improvement of stress urinary incontinence.	1b
Laparoscopic colposuspension has similar efficacy to open colposuspension for cure of stress urinary incontinence and a similar risk of voiding difficulty or <i>de novo</i> urgency.	1a
Laparoscopic colposuspension has a lower risk of other complications and shorter hospital stay than open colposuspension.	1a
Autologous fascial sling has a higher risk of operative complications than open colposuspension, particularly voiding dysfunction and post-operative urinary tract infection.	1b

4.3.1.5 *Bulking agents*

4.3.1.5.1 Question

In women with SUI, does injection of a urethral bulking agent cure SUI or improve QoL, or cause adverse outcomes?

4.3.1.5.2 Evidence

There have been two Cochrane systematic reviews [332, 333] and one independent systematic review [334], which reported on twelve RCTs or quasi-RCTs of injectable agents. In general, the trials were only of moderate quality and small, with many of them only being reported in abstract form. Wide confidence intervals meant a meta-analysis was not possible. Since the Cochrane review, two further RCTs have been reported [335, 336].

Each injectable product has been the subject of many case series. Short-term efficacy in reducing the symptoms of SUI has been demonstrated for all materials used. In 2006, NICE published an extensive review of these case series [50]. These case series have added very little to the evidence provided by RCTs. There has been only one placebo-controlled RCT, in which an autologous fat injection was compared with the placebo of a saline injection.

Comparison with open surgery

Two RCTs compared collagen injection to conventional surgery for SUI (autologous sling vs. silicon particles and collagen vs. assorted procedures). The studies reported greater efficacy but higher complication rates for open surgery. In comparison, collagen injections showed inferior efficacy but equivalent levels of satisfaction and fewer serious complications [50, 337].

Another trial found that a peri-urethral route of injection can carry a higher risk of urinary retention compared to a transurethral injection [338]. A recent small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [335].

Summary of evidence	LE
Peri-urethral injection of bulking agent may provide short-term improvement in symptoms (three months), but not cure, in women with stress urinary incontinence.	2a
Repeat injections to achieve therapeutic effect are often required.	2a
Bulking agents are less effective than colposuspension or autologous sling for cure of stress urinary incontinence.	2a
Adverse effect rates are lower compared to open surgery.	2a
There is no evidence that one type of bulking agent is better than another type.	1b
Transperineal route of injection may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

Recommendations	GR
Offer the mid-urethral sling to women with uncomplicated stress urinary incontinence as the preferred surgical intervention whenever available.	A
Warn women who are being offered a retropubic insertion of mid-urethral sling about the relatively higher risk of peri-operative complications compared to transobturator insertion.	A
Warn women who are being offered transobturator insertion of mid-urethral sling about the higher risk of pain and dyspareunia in the longer term.	A
Warn women who are being offered a single-incision sling that long-term efficacy remains uncertain.	A
Do a cystourethroscopy as part of the insertion of a mid-urethral sling.	C
Offer colposuspension (open or laparoscopic) or autologous fascial sling for women with stress urinary incontinence if mid-urethral sling cannot be considered.	A
Warn women undergoing autologous fascial sling that there is a high risk of voiding difficulty and the need to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.	C
Inform older women with stress urinary incontinence about the increased risks associated with surgery, including the lower probability of success.	B
Inform women that any vaginal surgery may have an impact on sexual function.	B
Only offer new devices, for which there is no level 1 evidence base, as part of a structured research programme.	A*
Only offer adjustable mid-urethral sling as a primary surgical treatment for stress urinary incontinence as part of a structured research programme.	A*
Do not offer bulking agents to women who are seeking a permanent cure for stress urinary incontinence.	A*

* Recommendation based on expert opinion.

4.3.2 Complicated stress urinary incontinence in women

This section will address surgical treatment for women who have had previous surgery for SUI, which has failed, or those women who have undergone previous radiotherapy affecting the vaginal or urethral tissues. Neurogenic LUT dysfunction is reviewed by the EAU Guidelines on Neuro-Urology [2]. Women with associated genitourinary prolapse are included in this edition (see section 4.3.3).

4.3.2.1 Colposuspension or sling following failed surgery

There may be persistent or recurrent SUI, or the development of *de novo* UUI. This means that careful evaluation including urodynamics becomes an essential part of the work-up of these patients.

4.3.2.1.1 Question

In women who have had failed surgery for SUI, what is the effectiveness of any second-line operation, compared to any other second-line operation, in terms of cure or improvement of UI, QoL or adverse events?

4.3.2.1.2 Evidence

Most of the data on surgery for SUI refer to primary operations. Even when secondary procedures have been included, it is unusual for the outcomes in this subgroup to be separately reported. When they are, the numbers of patients is usually too small to allow meaningful comparisons.

The 4th International Consultation on Incontinence includes a review of this topic [1] up to 2008, and the subject has also been reviewed by Ashok [339] and Lovatsis *et al.* [340]. A further literature review has been carried out since that time by the Panel.

Cochrane reviews of individual operative techniques have not included separate evaluation of outcomes in women undergoing second-line surgery. However, there is a current protocol to address this issue [341]. Only one RCT was found (abstract only) comparing TVT to laparoscopic colposuspension in women with recurrent SUI. This small study found similar cure rates and adverse events in the short term for both procedures [315].

Post-hoc subgroup analysis of high-quality RCTs comparing one procedure to another have shown conflicting evidence of relative effectiveness [74, 325, 342, 343]. One large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for fascial sling [344].

Several cohort studies have reported outcomes for TVT specifically for primary and secondary cases. Evidence on the effectiveness of second-line retropubic tapes conflicts with some series showing equivalent outcomes for primary and secondary cases [345, 346], whilst other research has shown inferior outcomes for secondary surgery [347, 348]. Other confounding variables make meaningful conclusions difficult.

Systematic review of older trials of open surgery for SUI suggest that the longer-term outcomes of redo open colposuspension may be poor compared to autologous fascial slings [349]. Successful results have been reported from mid-urethral slings after various types of primary surgery, while good outcomes are reported for both repeat TVT and for 'tightening' of TVT, but data are limited to small case series only.

Summary of evidence	LE
There is conflicting evidence whether prior surgery for stress incontinence or prolapse results in inferior outcomes from repeat operations for stress urinary incontinence.	2
Most procedures will be less effective when used as a second-line procedure than when used for primary surgery.	2
In women who have had more than two procedures for stress urinary incontinence, the results of open colposuspension are inferior to autologous fascial sling.	2

4.3.2.2 External compression devices

External compression devices are still widely used in the treatment of recurrent SUI after the failure of previous surgery and if there is thought to be profound intrinsic failure of the sphincter mechanism, characterised by very low leak point pressures or low urethral closure pressures. This should be confirmed by urodynamic evaluation.

The two intracorporeal external urethral compression devices available are the adjustable compression therapy (ACT) device and the artificial urinary sphincter (AUS). Using ultrasound or fluoroscopic guidance, the ACT device is inserted by placement of two inflatable spherical balloons on either side of the bladder neck. The volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. More recently, an adjustable artificial urinary sphincter (Flowsecure™) has been introduced. It has the added benefit of 'conditional occlusion', enabling it to respond to rapid changes in intra-abdominal pressure.

4.3.2.2.1 Questions

- In women with SUI, does insertion of an external compressive device cure SUI, improve QoL or cause adverse outcomes?
- How do external compression devices compare to other surgical treatments for SUI?

4.3.2.2.2 Evidence

The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally [111]. However, voiding dysfunction is a known side effect, with a lack of data making it difficult to assess its importance. Because of significant differences in design between devices and in selection criteria between case series, results obtained with specific devices cannot be extrapolated generally to the use of adjustable devices. A recent consensus report has standardised the terminology used for reporting complications arising from implantation of materials into the pelvic floor region [17].

Artificial urinary sphincter (AUS)

A previous review of mechanical devices concluded that there was insufficient evidence to support the use of AUS in women [350].

There are a few case series in women, including four series (n = 611), with study populations ranging from 45 to 215 patients and follow-up ranging from one month to 25 years [351-354]. Case series have been confounded by varying selection criteria, especially the proportion of women who have neurological dysfunction or who have had previous surgery. Most patients achieved an improvement in SUI, with reported subjective cures in 59-88%. Common side effects included mechanical failure requiring revision (up to 42% at ten years) and explantation (5.9-15%). In a retrospective series of 215 women followed up for a mean of six years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [354]. Peri-operative injury to the urethra, bladder or rectum was also a high-risk factor for explantation [352].

A newly introduced artificial sphincter using an adjustable balloon capacity through a self-sealing port, and stress responsive design, has been introduced to clinical use. A series of 100 patients reported 28% explantation at four years but the device has undergone redesign and more up-to-date evidence is awaited [355]. Early reports of laparoscopically implanted AUS do not have sufficient patient populations and/or sufficient follow-up to be able to draw any conclusions [356, 357].

Adjustable compression device (ACT)

There are four case series (n = 349), with follow-up ranging from five to 84 months [358-361]. Reported outcome ranged from 47% objective cure to 100% subjective improvement. However, most patients required adjustment to achieve continence and 21% required explantation.

Summary of evidence	LE
Implantation of an artificial sphincter can improve or cure incontinence in women with stress urinary incontinence caused by sphincter insufficiency.	3
Implantation of the adjustable compression therapy (ACT) device may improve complicated urinary incontinence.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the adjustable compression device.	3
Explantation is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

Recommendations	GR
Management of complicated stress urinary incontinence should only be offered in expert** centres.	A*
The choice of surgery for recurrent stress urinary incontinence should be based on careful evaluation of the individual patient including multichannel urodynamics and imaging as appropriate.	C
Warn women with recurrent stress urinary incontinence that the outcome of a surgical procedure, when used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications.	C
Consider secondary synthetic sling, colposuspension or autologous sling as first options for women with complicated stress urinary incontinence.	C
Warn women receiving artificial urinary sphincter or ACT device that, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	C

* Recommendation based on expert opinion.

** Expert centres refers to the comments on surgeon volume in the introduction to the surgical chapter.

4.3.3 Women with both stress urinary incontinence and pelvic organ prolapse

There is a clear association between the presence of POP and SUI. Although the subject of prolapse is not part of the remit of these Guidelines, the extent to which it impacts on the management of SUI will be addressed. The aim is to assess the options available to women who require surgery for POP and who have associated UI (either symptomatic or after reduction of prolapse), and to assess the value of prophylactic anti-incontinence surgery in women with no evidence of UI.

4.3.3.1 Questions

1. In women with POP and UI, does combined surgery for POP and SUI reduce the incidence of post-operative UI compared to POP surgery alone?

2. In continent women with POP, does combined surgery for POP and SUI reduce the incidence of post-operative *de novo* UI compared to POP surgery alone?
3. In women with POP and occult SUI, (i.e. seen only on prolapse reduction stress testing/ urodynamics), does combined surgery for POP and SUI reduce the incidence of post-operative UI compared to POP surgery alone?
4. In women with POP and OAB, does surgery for POP improve OAB symptoms?
5. In adults with POP, what is the reliability, the diagnostic accuracy and predictive value of a prolapse reduction test to identify patients at risk from *de novo* SUI following prolapse repair?

4.3.3.2 Evidence

A Cochrane review in 2013 included sixteen trials concerning bladder function after surgery for pelvic organ prolapse [362]. After prolapse surgery 434 of 2125 women (20.4%) reported new subjective SUI, in sixteen trials. New voiding dysfunction was reported in 109 of 1,209 (9%) women, in twelve trials.

1. In women with POP does combined surgery for POP and SUI reduce the incidence of post-operative UI compared to POP surgery alone?

There are two well-designed RCTs relating to the prevalence of post-operative SUI in women who underwent prolapse surgery with and without an anti-incontinence procedure. Both of these trials involved women with POP who did not complain of symptoms of stress incontinence regardless of objective findings.

One trial compared abdominal sacrocolpopexy with and without Burch colposuspension [363], the other compared vaginal repair with and without a mid-urethral sling [364]. In both trials addition of an anti-incontinence surgery reduced the risk of SUI at twelve months. In one trial there was a higher rate of adverse events reported in the combined surgery group [364]. This was also the finding of the Cochrane review and meta-analysis.

Two trials addressed post-operative SUI in patients who had had SUI pre-operatively. Borstad *et al.*, in a multicentre trial, randomised women with POP and SUI to have a tension-free vaginal tape (TVT) at the time of prolapse repair or three months later, if they still had SUI. (n = 53). One year after surgery there was no difference between the groups regarding continence; however, 44% of the women without initial TVT never required surgery and 29% were dry [365].

In contrast, Costantini *et al.* followed-up women with POP and SUI randomised to abdominal POP repair with or without Burch colposuspension (after a median of 97 months), finding that additional SUI surgery did not improve outcome [366]. On the contrary, a higher number of patients had *de novo* storage symptoms when a Burch colposuspension was performed.

In summary, it is difficult to generalise the results of trials using very different procedures to treat both POP and UI. It seems that with a combined procedure the rate of SUI post-operatively is lower. Studies using midurethral slings have generally shown more significant differences in UI outcomes with combined procedures than when other types of anti-incontinence procedure have been used. Individual patient characteristics may play the most important role in shaping treatment decisions. It must be taken into account that, although more women may be dry after combined surgery, the risks of repeat surgery, should it become necessary, may outweigh the potential benefits.

2. Continent women with POP

The 2013 Cochrane review included 6 trials showing that post-operative incontinence rates at < twelve months were 19% in the combined surgery group vs. 32% in POP surgery alone. In this group of 438 women, undergoing continence surgery at the time of prolapse prevented 62 (14%) women from developing *de novo* SUI post-prolapse surgery. A long-term update of a previously published RCT comparing POP surgery with or without Burch colposuspension in continent women suggested higher UI rates in women undergoing colposuspension [364].

3. Women with POP and occult SUI

The 2013 Cochrane review included five trials addressing this point. Overall, there was a significantly higher rate of post-operative patient-reported SUI with prolapse surgery alone than compared with combined surgery.

4. Women with POP and OAB

There are three case series evaluating patients with concomitant OAB and pelvic organ prolapse which

assess incontinence/OAB symptom scores post-surgical repair. Costantini *et al.* assessed the effect of posterior repair on OAB/DO and reported a 70-75% improvement rate in both parameters along with a 93% anatomic success rate [367]. Kummeling *et al.* assessed the effect of a modified laparoscopic sacrocolpopexy on urodynamic parameters and reported an improvement with no evidence to support a concomitant prophylactic colposuspension [368]. Lee *et al.* assessed the value of pre-op urodynamic study and bladder outlet obstruction index (BOOI) in predicting the degree of OAB symptoms post anterior prolapse repair. They reported a significant correlation between low pre-op BOOI and improvement in OAB symptom scores post-op [369].

5. Prolapse reduction stress test (PRST)

Data concerning PRST were made available from the CARE trial, where significant differences were noted in the detection of urodynamic stress incontinence with prolapse reduction among the various methods studied, ranging from 6% (pessary) to 30% (speculum). Manual, swab and forceps showed detection rates of 16%, 20% and 21%, respectively [370]. In the study by Duecy, about one third of women were diagnosed with occult SUI using a pessary while two thirds were diagnosed with manual reduction of the prolapse [371]. In a further study occult SUI was only detected by a pessary test in 19% of patients, not by urodynamics, history or clinical examination [372].

Summary of evidence	LE
Women with prolapse + urinary incontinence	
Surgery for pelvic organ prolapse (POP) + stress urinary incontinence shows a higher rate of cure of urinary incontinence in the short term than POP surgery alone.	1a
There is conflicting evidence on the relative long-term benefit of surgery for POP + stress urinary incontinence vs. POP surgery alone.	1b
Combined surgery for POP + stress urinary incontinence carries a higher risk of adverse events.	1b
Continent women with pelvic organ prolapse	
Are at risk of developing urinary incontinence post-operatively.	1a
The addition of a prophylactic anti-incontinence procedure reduces the risk of post-operative urinary incontinence.	1b
The addition of a prophylactic anti-incontinence procedure increases the risk of adverse events.	1b
Women with pelvic organ prolapse and overactive bladder	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of overactive bladder.	3
Surgery for POP + occult stress urinary incontinence shows a higher rate of cure of occult stress urinary incontinence in the short term than POP surgery alone.	1a
Combined surgery for POP + stress urinary incontinence carries a higher risk of adverse events than POP surgery alone.	1b

Recommendations for women requiring surgery for bothersome pelvic organ prolapse who have symptomatic or unmasked stress urinary incontinence	GR
Offer simultaneous surgery for pelvic organ prolapse and stress urinary incontinence.	A
Warn women of the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	A
Recommendations for women requiring surgery for bothersome pelvic organ prolapse without symptomatic or unmasked stress urinary incontinence.	
Warn women that there is a risk of developing <i>de novo</i> stress urinary incontinence after prolapse surgery.	A
Inform women that the benefit of prophylactic stress urinary incontinence surgery is uncertain.	C
Warn women that the benefit of surgery for stress urinary incontinence may be outweighed by the increased risk of adverse events with combined surgery compared to prolapse surgery alone.	A

4.3.4 Urethral diverticulum

A female urethral diverticulum is a sac-like protrusion made up by the entire urethral wall or only by the urethral mucosa situated between the periurethral tissues and the anterior vaginal wall. Urethral diverticulum give rise to a variety of symptoms that include pain, urgency, frequency, recurrent UTIs, vaginal discharge, dyspareunia, voiding difficulties or urinary incontinence.

4.3.4.1 Question

In a woman with the clinical suspicion of having a urethral diverticulum, what is the best test to confirm the diagnosis?

4.3.4.2 Evidence

No robust diagnostic accuracy studies address this question. However, a case series of 27 patients concluded that endoluminal (vaginal or rectal) MRI has better diagnostic accuracy than voiding cystourethrography (VCUG) [373]. In a case series of 60 subjects Pathi, *et al.* reported that the sensitivity, specificity, positive predictive value and negative predictive value of MRI is 100%, 83%, 92% and 100%, respectively [374]. Dwarkasing *et al.* also reports 100% specificity and sensitivity of MRI in a case series of 60 patients [375]. However, in a case series of 41 patients, a study reported 25% discrepancy between MRI and surgical findings [376].

4.3.4.3 Question

In a woman who has a bothersome urethral diverticulum, what is the relative effectiveness of available surgical treatments?

4.3.4.4 Surgical treatment

No RCTs were found. Surgical removal is the most commonly reported treatment in contemporary case series. However, recurrence may occur; Han *et al.* found a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticulum within one year [377], Ingber *et al.* found a 10.7% recurrence rate in 122 women undergoing diverticulectomy, with a higher risk of recurrence in those with proximal or multiple diverticula or after previous pelvic surgery [378]. SUI may occur in up to 20% of women after diverticulectomy, requiring additional correction [379-382]. *De novo* SUI seems to be more common in proximal and in large size (> 30 mm) diverticula.

Diverticula may undergo neoplastic alterations (6%) including invasive adenocarcinomas [383].

Summary of evidence	LE
Magnetic resonance imaging has good sensitivity and specificity for the diagnosis of urethral diverticula; however, there is a risk of misdiagnosis and missing potential intraluminal neoplastic change.	3
Surgical removal of symptomatic urethral diverticula provides good long-term results; however, women should be counselled of the risk of recurrence and <i>de novo</i> stress urinary incontinence.	3

Recommendation	GR
Symptomatic urethral diverticula should be completely surgically removed.	A*

* Recommendation based on expert opinion.

4.3.5 Men with stress urinary incontinence

In men who fail conservative treatment (see chapter 4.1.3.3.5) other treatments can be considered.

4.3.5.1 Drug therapy

Three RCTs suggest an earlier recovery of continence in men receiving duloxetine either alone [384], or in addition to PFMT, for post prostate surgery SUI [385, 386].

Summary of evidence	LE
Duloxetine, either alone or combined with conservative treatment, can hasten recovery of continence but does not improve continence rate following prostate surgery.	1b

4.3.5.2 Bulking agents in men

Injection of bulking agents has been used to try and improve the coaptation of a damaged sphincter zone. Initial reports showed limited efficacy in treating incontinence following radical prostatectomy incontinence [387, 388].

4.3.5.2.1 Question

In men with post-prostatectomy incontinence or SUI, does injection of a urethral bulking agent cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.2.2 Evidence

Most studies are case series with small sample sizes. Small cohort studies showed a lack of benefit using a number of different materials [389, 390]. However, polyacrylamide hydrogel resulted in limited improvement in QoL without curing the UI [389]. A Cochrane review on the surgical treatment of post-prostatectomy incontinence found only one study that fulfilled the inclusion criteria [391]. A prospective, randomised study compared the AUS to silicon particles (Macroplastique™) in 45 patients. Eighty-two per cent of patients receiving an AUS were continent compared to 46% receiving silicone particles. In patients with severe incontinence, outcome was significantly worse after silicon bulking injection.

Summary of evidence	LE
There is no evidence that bulking agents cure post-prostatectomy incontinence.	2a
There is weak evidence that bulking agents can offer temporary, short-term, improvement in QoL in men with post-prostatectomy incontinence.	3
There is no evidence that one bulking agent is superior to another.	3

4.3.5.3 Fixed male sling

In addition to external compression devices and bulking agents, slings have been introduced to treat post-prostatectomy incontinence. Fixed slings are positioned under the urethra and fixed by a retropubic or transobturator approach. The tension is adjusted during the surgery and cannot be re-adjusted post-operatively.

For the restoration of continence by these male slings, two concepts are now being proposed:

- continence restoration by urethral compression (InVance®, Istop TOMS, Argus®);
- continence restoration by repositioning the bulb of urethra (AdVance™) [392].

In principle, the AUS can be used for all degrees of post-prostatectomy incontinence, while male slings are advocated for mild-to-moderate UI. However, the definitions of mild and moderate UI are not clear. The definition of cure, used in most studies, was no pad use or one security pad per 24 hours. Some authors used a stricter criterion of less than 2 g urine loss in a 24-hour pad test [393].

4.3.5.3.1 Question

In men with post-prostatectomy SUI, does insertion of a fixed suburethral sling cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.3.2 Evidence

Concerning the surgical treatment of post-prostatectomy incontinence, three recent literature reviews are available [394-396]. There are a large number of uncontrolled case series concerning men implanted with several types of slings [397, 398].

For the repositioning sling (AdVance™), the benefit after a mean follow-up of three years has been published on 136 patients [399]. Earlier data were available from other cohort studies, totalling at least 614 patients with a mean follow-up of between three months and three years. Subjective cure rates for the device vary between 8.6% and 73.7%, with a mean of 49.5%. Radiotherapy was a negative prognostic factor [397]. Post-operative voiding dysfunction occurred in 5.7-1.3%, while erosions and chronic pain were uncommon (0-0.4%) [393, 399-401]. The overall failure rate was about 20%.

The previously available 'InVance®' device has now been removed from the market in some countries.

Summary of evidence	LE
There is limited short-term evidence that fixed male slings cure or improve post-prostatectomy incontinence in patients with mild-to-moderate incontinence.	3
Men with severe incontinence, previous radiotherapy or urethral stricture surgery may have less benefit from fixed male slings.	3
There is no evidence that one type of male sling is better than another.	3

4.3.5.4 Adjustable slings in males

Adjustability in male sling surgery attempts to adjust the tension of the sling post-operatively. Three main systems have been used in men: the Remeex[®] system, the Argus[®] system and the ATOMS[®] system.

4.3.5.4.1 Question

In men with post-prostatectomy incontinence or SUI, does insertion of an adjustable suburethral sling cure or improve SUI, improve QoL, or cause adverse outcomes?

4.3.5.4.2 Evidence

There are no RCTs. Most studies consist of prospective or retrospective case series, with variable follow-up and different definitions of success. Some have been published only as conference abstracts.

For the Remeex[®] system, only two abstracts, with conflicting findings, have been published. One study followed nineteen patients for nearly seven years and reported 70% success, with no explants, infections or erosions. The second study followed fourteen patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% [402].

Argus[®] system

Data on the Argus[®] system has been reported for 404 men, but only four series have reported on more than 50 patients [403, 404], with the longest follow-up being 2.4 years. Success rates varied between 17% and 91.6%, with a mean of 57.6% predominantly reporting a subjective cure. The number of implants requiring re-adjustment was reported as between 22.9% and 41.5% [404]. Infection of the device occurred in 5.4-8% [403]. Erosions were reported in 5-10% [405]. Urethral perforations occurred in 2.7-16% [403]. Pain at the implant site was usually only temporary, but chronic pain has been reported [403, 405]. These complications resulted in explantation rates of 10-15% [404].

The ATOMS[®] system consists of a mesh implant with an integrated adjustable cushion, which uses a titanium port left in the subcutaneous tissue of the lower abdomen or scrotum for adjustment of cushion volume. Initial reports show objective cure rates of 60.5% and improvement rates of 23.7% but with the need for up to nine post-operative adjustments [406, 407].

Summary of evidence	LE
There is limited evidence that adjustable male slings can cure or improve stress urinary incontinence in men.	3
There is limited evidence that early explantation rates are high.	3
There is no evidence that adjustability of the male sling offers additional benefit over other types of sling.	3

4.3.5.5 Compression devices in males

External compression devices can be divided into two types: circumferential and non-circumferential compression of the urethral lumen [394]. The artificial urinary sphincter (AUS) is the standard treatment for moderate-to-severe male SUI. Most data available on the efficacy and adverse effects of AUS implantation are from older retrospective cohort studies with RCTs not performed due to the lack of a comparator. Men considering insertion of an AUS should understand that if the ability of an individual to operate the pump is uncertain, it may not be appropriate to implant an AUS. There are several recognised complications of AUS implantation, e.g. mechanical dysfunction, urethral constriction by fibrous tissue, erosion and infection. The non-circumferential compression devices consist of two balloons placed close to the vesico-urethral anastomotic site. The balloons can be filled and their volume can be adjusted post-operatively through an intra-scrotal port. Men who develop cognitive impairment or lose manual dexterity will have difficulty operating an AUS.

4.3.5.5.1 Question

In men with post-prostatectomy SUI, does insertion of an external compression device cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.5.2 Evidence

Artificial urinary sphincter

Although the AUS is considered to be the standard treatment for men with SUI, there are two systematic reviews [391, 396] presenting limited evidence, of generally poor quality, except for one RCT comparing AUS with bulking agents [387]. A continence rate of about 80% can be expected, while this may be lower in men

who have undergone pelvic radiotherapy [394].

Trigo Rocha *et al.* published a prospective cohort study on 40 patients with a mean follow-up of 53 months, showing that from all urodynamic parameters only low bladder compliance had a negative impact on the outcome [408]. Another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [409].

The transcorporeal technique of placement can be used for repeat surgery but evidence of effectiveness is lacking [410]. The dual-cuff placement was introduced to treat patients who remained incontinent with a single 4 cm cuff in place. However, it has not improved control of UI, while the availability of a 3.5 cm cuff may have eliminated the need for a dual cuff [411, 412]. Patients who experienced complete continence after AUS implantation had a higher erosion risk [413]. One small series reported results of AUS implantation after failure of previous AdVance™ sling, showing no difference in efficacy between secondary and primary implantation [414].

Non-circumferential compression device (ProAct®)

There have been trials to treat post-prostatectomy SUI by insertion of a device consisting of balloons with adjustable volume external to the proximal bulbar urethra. A prospective cohort study (n = 128) described the functional outcome as 'good' in 68%, while 18% of the devices had to be explanted [415]. A subgroup of radiotherapy patients only had 46% success and a higher percentage of urethral erosions.

A quasi-randomised trial comparing a non-circumferential compression device (ProAct®) with bone-anchored male slings found that both types of device resulted in similar improvement of SUI (68% vs. 65%, respectively) [416]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [396, 417-420]. A questionnaire study showed that 50% of patients were still bothered significantly by persistent incontinence [421]. Other designs of artificial sphincter remain the subject of ongoing evaluation though they may have been introduced onto the market.

Summary of evidence	LE
There is evidence that primary artificial urinary sphincter (AUS) implantation is effective for cure of stress urinary incontinence in men.	2b
Long-term failure rate for AUS is high although device replacement can be performed.	3
There are conflicting data on whether previous pelvic radiotherapy affects the outcome of AUS implantation.	3
The usefulness of tandem-cuff placement is uncertain.	3
There is insufficient evidence to state whether one surgical approach for cuff placement is superior to another.	3
Very limited short-term evidence suggests that the non-circumferential compression device (ProACT®) is effective for treatment of post-prostatectomy stress urinary incontinence.	3
The non-circumferential compression device (ProACT®) is associated with a high failure and complication rate leading to frequent explantation.	3
The rate of explantation of the AUS because of infection or erosion remains high (up to 24% in some series).	3
Mechanical failure is common with the AUS.	3
Revision and re-implantation of AUS is possible after previous explantation or for mechanical failure.	3

Recommendations	GR
Consider offering duloxetine to hasten recovery of continence after prostate surgery but inform the patient about the possible adverse events.	B
Only offer bulking agents to men with mild post-prostatectomy incontinence who desire temporary relief of incontinence symptoms.	C
Do not offer bulking agents to men with severe post-prostatectomy incontinence.	C
Offer fixed slings to men with mild-to-moderate* post-prostatectomy incontinence.	B
Warn men that severe incontinence, prior pelvic radiotherapy or urethral stricture surgery, may worsen the outcome of fixed male sling surgery.	C
Offer AUS to men with moderate-to-severe post-prostatectomy incontinence.	B
Implantation of AUS or artificial compression device (ACT) for men should only be offered in expert centres.	C

Warn men receiving AUS or ACT that, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	C
Do not offer non-circumferential compression device (ProACT [®]) to men who have had pelvic radiotherapy.	C

* The terms mild and moderate post-prostatectomy incontinence remain undefined.

4.3.6 Surgical interventions for refractory detrusor-overactivity

4.3.6.1 Bladder wall injection of botulinum toxin A

Onabotulinum toxin A (onabotA; BOTOX[®]) 100 U dissolved in 10 mL of saline and injected in 20 points of the bladder wall above the trigone (0.5 mL per injection site) is licenced in Europe to treat OAB with persistent or refractory UUI in adults of both gender, despite the small number of males included in the registration trials [422, 423]. Surgeons must realise that other doses of onabotA and other formulations of botulinum toxin A, abobotulinum toxinA and incobotulinum toxin A, are not licensed for use in UUI. Doses for onabotA are not transposable to the other brands of botulinum toxin A. The continued efficacy of repeat injections is the rule but discontinuation rate may be high. The most important adverse events related to onabotA 100 U injection detected in the regulatory trials were UTI and an increase in PVR that may require clean intermittent catheterisation [424].

4.3.6.1.1 Question

In adults with UUI, is bladder wall injection of onabotA better than no treatment for cure or improvement?

4.3.6.1.2 Evidence

Following a dose ranging study in which the 100 U of onabotA was established as the ideal dose, two phase III trials randomised (1:1) 1,105 OAB incontinent patients whose symptoms were not adequately managed with anticholinergics to receive bladder wall injections of onabotA (100 U) or saline. At baseline the population had on average more than five episodes of UUI, around twelve micturitions per day and small PVR. At week twelve, in patients treated with onabotA UUI episodes/day were halved and number of micturitions/day reduced by more than two. A total of 22.9% of the patients in the onabotA arm were fully dry, against 6.5% in the saline arm [425].

Quality of life was substantially improved in the onabotA arm, as shown by the more than 60% of positive responses in the TBS questionnaire at week twelve, which was double the positive responses in the saline arm. Cohort studies have shown the effectiveness of bladder wall injections of onabotA in the elderly and frail elderly [426], though the success rate might be lower and the PVR (> 150 mL) higher in this group.

The median time to request retreatment in the pooled analysis of the two RCTs was 24 weeks [424, 425].

A recent RCT compared onabotA injection 100 U to solifenacin (with dose escalation or switch to trospium possible in the solifenacin group) and showed similar rates of improvement in UUI over the course of six months [427]. However, patients receiving onabotA were not only more likely to have cure of UUI (27% vs. 13%, $p = 0.003$), but also had higher rates of urinary retention during the initial two months (5% vs. 0%) and of UTIs (33% vs. 13%). Patients taking antimuscarinics were more likely to have dry mouth.

Identification of DO in urodynamics does not influence the outcome of onabotulinum toxin A injections in patients with UUI [58].

Summary of evidence	LE
A single treatment session of onabotulinum toxin A (100 U) injected in the bladder wall is more effective than placebo at curing and improving urgency urinary incontinence and QoL.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy.	3
There is a high risk of increased post-void residual when injecting elderly frail patients.	3
The risk of bacteriuria after onabotulinum toxin A (100 U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A (100 U) is superior to solifenacin for cure of urgency urinary incontinence, but rates of improvement were equivalent.	1b

Recommendations	GR
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with urgency urinary incontinence refractory to conservative therapy (such as pelvic floor muscle training and/or transdermal drug treatment).	A
Warn patients of the limited duration of response, risk of urinary tract infection and the possible prolonged need to self-catheterise (ensure that they are willing and able to do so).	A

4.3.6.2 Sacral nerve stimulation (neuromodulation)

In the first stage of a two-stage implantation, an electrode is placed percutaneously under fluoroscopic control in the sacral foramen alongside a sacral nerve, usually S3. In earlier techniques, a temporary wire electrode was used. More recently, a permanent tined electrode has been used for a longer test phase. Patients, in whom selected symptoms of UUI are reduced by more than 50% during the test phase, are candidates for the full implant, including the pulse generator and reported results only apply to this sub population.

4.3.6.2.1 Question

In adults suffering from refractory UUI, what is the clinical effectiveness of sacral nerve neuromodulation compared to alternative treatments?

4.3.6.2.2 Evidence

All randomised studies suffer from the limitation that assessors and patients were not blind to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. A Cochrane review of the literature until March 2008 [428] identified three RCTs that investigated sacral nerve stimulation in patients with refractory UUI.

One study compared implantation to controls who stayed on medical treatment and received delayed implantation at six months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at six months compared to 1.6% of the control group [429]. The other RCT [430] achieved similar results, although these patients had already been included in the first report [429]. However, Weil *et al.* [430] showed that the effect on generic QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions.

The results of seventeen case series of patients with UUI, who were treated early in the experience with sacral nerve stimulation, were reviewed [431]. After a follow-up duration of between one and three years, approximately 50% of patients with UUI demonstrated > 90% reduction in UI, 25% demonstrated 50-90% improvement, and another 25% demonstrated < 50% improvement. Two case series describing the outcome of sacral nerve neuromodulation, with a mean or median follow-up of at least four years [432, 433] reported continued success (> 50% improvement on original symptoms) in patients available for follow-up. Cure rates for UUI were 15% [433].

Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33-41% [432, 433]. In a subanalysis of the RCT, the outcomes of UUI patients, with or without pre-implant DO, were compared. Similar success rates were found in patients with and without urodynamic DO [434].

Summary of evidence	LE
Sacral nerve neuromodulation is more effective than continuation of failed conservative treatment for cure of urgency urinary incontinence, but no sham controls have been used.	1b
In those patients who have been implanted, at long-term, 50% improvement of urgency urinary incontinence is maintained in at least 50% of patients and 15% may remain cured.	3
The use of tined, permanent electrodes in a staged approach results in more patients receiving the final implant than occurs with temporary test stimulation.	4

Recommendation	GR
Offer sacral nerve modulation to patients who have urgency urinary incontinence refractory to antimuscarinic therapy.	A

4.3.6.2.3 Research priority

An RCT comparing a strategy of botulinum toxin injection, repeated as required, against a strategy of test and permanent sacral nerve neuromodulation, with accompanying health economic analysis, is ongoing.

4.3.6.3 Cystoplasty/urinary diversion

4.3.6.3.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. The distal ileum is the bowel segment most often used but any bowel segment can be used if it has the appropriate mesenteric length. One study did not find any difference between bivalving the bladder in the sagittal or in the coronal plane [435, 436].

There are no RCTs comparing bladder augmentation to other treatments for patients with UUI. Most often, bladder augmentation is used to correct neurogenic DO or small-capacity, low-compliant, bladders caused by fibrosis, tuberculosis, radiation or chronic infection.

The largest case series of bladder augmentation in a mixed population of idiopathic and neurogenic UUI included 51 women [437]. At an average follow-up of 74.5 months, only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. It seems that the results for patients with idiopathic DO (58%) appeared to be less satisfactory than for patients with neurogenic UUI (90%).

Adverse effects were common and have been summarised in a review over five to seventeen years of more than 267 cases, 61 of whom had non-neurogenic UUI [438]. In addition, many patients may require clean intermittent self-catheterisation to obtain adequate bladder emptying (Table 3).

Table 3: Complications of bladder augmentation

Short-term complications	Affected patients (%)
Bowel obstruction	2
Infection	1.5
Thromboembolism	1
Bleeding	0.75
Fistula	0.4
Long-term complications	Affected patients (%)
Clean intermittent self-catheterisation	38
Urinary tract infection	70% asymptomatic; 20% symptomatic
Urinary tract stones	13
Metabolic disturbance	16
Deterioration in renal function	2
Bladder perforation	0.75
Change in bowel symptoms	25

4.3.6.3.2 Detrusor myectomy (bladder auto-augmentation)

Detrusor myectomy aims to increase bladder capacity and reduce storage pressures by incising or excising a portion of the detrusor muscle, to create a bladder mucosal 'bulge' or pseudo-diverticulum. It was initially described as an alternative to bladder augmentation in children [439]. Two case series [440, 441] in adult patients with idiopathic and neurogenic bladder dysfunction, demonstrated poor long-term results caused by fibrosis of the pseudo-diverticulum. This technique is rarely, if ever, used nowadays.

4.3.6.3.3 Urinary diversion

Urinary diversion remains a reconstructive option for patients who decline repeated surgery for UI. However, there are no studies that have specifically examined this technique in the treatment of non-neurogenic UI [435].

Summary of evidence	LE
There is limited evidence on the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic detrusor overactivity.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short-term and long-term severe complications.	3

The need to perform clean intermittent self-catheterisation following augmentation cystoplasty is very common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty with urinary diversion.	3
Detrusor myectomy is ineffective in adults with urinary incontinence.	3

Recommendations	GR
Only offer augmentation cystoplasty to patients with detrusor overactivity incontinence who have failed conservative therapy, in whom the possibility of botulinum toxin and sacral nerve stimulation has been discussed.	C
Warn patients undergoing augmentation cystoplasty of the high risk of having to perform clean intermittent self-catheterisation; ensure they are willing and able to do so.	C
Do not offer detrusor myectomy as a treatment for urinary incontinence.	C
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of urinary incontinence and who will accept a stoma.	C
Warn patients undergoing augmentation cystoplasty or urinary diversion of the high risk of short-term and long-term complications, and the possible small risk of malignancy.	C
Lifelong follow-up is mandatory in patients who have undergone augmentation cystoplasty or urinary diversion.	C

4.3.7 **Surgery in patients with mixed urinary incontinence**

4.3.7.1 *Question*

In adults with MUI, is the outcome of surgery different to that obtained with the same treatment in patients with either pure SUI or pure UUI?

4.3.7.2 *Evidence*

Many RCTs include both patients with pure SUI or pure UUI and patients with MUI. However, very few RCTs report separate outcomes for MUI and pure UI groups.

Transvaginal obturator tape

In an RCT including 96 women with MUI, objective improvement was better for patients treated with transvaginal obturator tape + the Ingelman Sundberg operation vs. patients treated with obturator tape alone [442].

Post-hoc analysis of the SISTER trial showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of pre-operative urgency [325]. A similar post-hoc review of another RCT comparing transobturator and retropubic mid-urethral slings showed that the greater the severity of pre-operative urgency the more likely that treatment would fail [74]. However, an earlier study had found that surgery provided similar outcomes, whether or not urgency was present prior to surgery (this study included only a few patients with urodynamic DO).

Case series tend to show poorer results in patients with MUI compared with those with pure SUI. In a case series of 192 women undergoing mid-urethral sling insertion, overall satisfaction rates were lower for women with mixed symptoms and detrusor overactivity on pre-operative urodynamics compared to those with pure SUI and normal urodynamics (75% vs. 98%, respectively) [443]. A comparison of two parallel cohorts of patients undergoing surgery for SUI, with and without DO, found inferior outcomes in women with MUI [444].

One cohort of 450 women, showed that in urgency-predominant MUI, the success rate fell to 52% compared to 80% in stress-predominant MUI [445]. In a study with 1,113 women treated with transvaginal obturator tape, SUI was cured equally in stress-predominant MUI or urgency-predominant MUI. However, women with stress-predominant MUI were found to have significantly better overall outcomes than women with urgency predominant MUI [446].

Overall, the outcome for women with pre-existing urgency incontinence remains uncertain.

Summary of evidence	LE
Women with mixed urinary incontinence are less likely to be cured of their urinary incontinence by stress urinary incontinence surgery than women with stress urinary incontinence alone.	1b
The response of pre-existing urgency symptoms to stress urinary incontinence surgery is unpredictable and symptoms may improve or worsen.	3

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Warn patients with mixed urinary incontinence that surgery is less likely to be successful than surgery in patients with stress urinary incontinence alone.	A
Warn patients with mixed urinary incontinence that one single treatment may not cure urinary incontinence; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	A*

* Upgraded following panel consensus.

4.3.7.3 Research priorities

Research trials should define accurately what is meant by 'mixed urinary incontinence'.

There is a need for well-designed trials comparing treatments in populations with MUI, and in which the type of MUI has been accurately defined.

4.3.8 Surgery for urinary incontinence in the elderly

There are no RCTs comparing surgical treatment in older vs. younger women although subgroup analyses of some RCTs have included a comparison of older with younger cohorts.

An RCT of 537 women comparing retropubic to transobturator tape, showed that cure rates decreased and failure increased with each decade over the age of 50 [447]. An RCT assessing risk factors for failure of tension free vaginal tape (TVT) vs. transobturator tension-free vaginal tape (TVT-O) in 162 women found that age is a specific risk factor (adjusted OR 1.7 per decade) for recurrence at one year [324]. In a subanalysis of the SISTER trial cohort of 655 women at 2 years of follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR 3.7, 95% CI 1.7-7.97), are less likely to report objective or subjective improvement in stress and urgency UI, and are more likely to undergo retreatment for SUI (OR 3.9, 95% CI 1.3-11.48). There was no difference in time to normal post-operative voiding [325].

Another RCT compared immediate TVT vs. delayed TVT in older women, confirming significant efficacy for the women operated upon, but the cohort as a whole suffered higher complication rates, particularly bladder perforation (22%) and urinary retention (13%) [326].

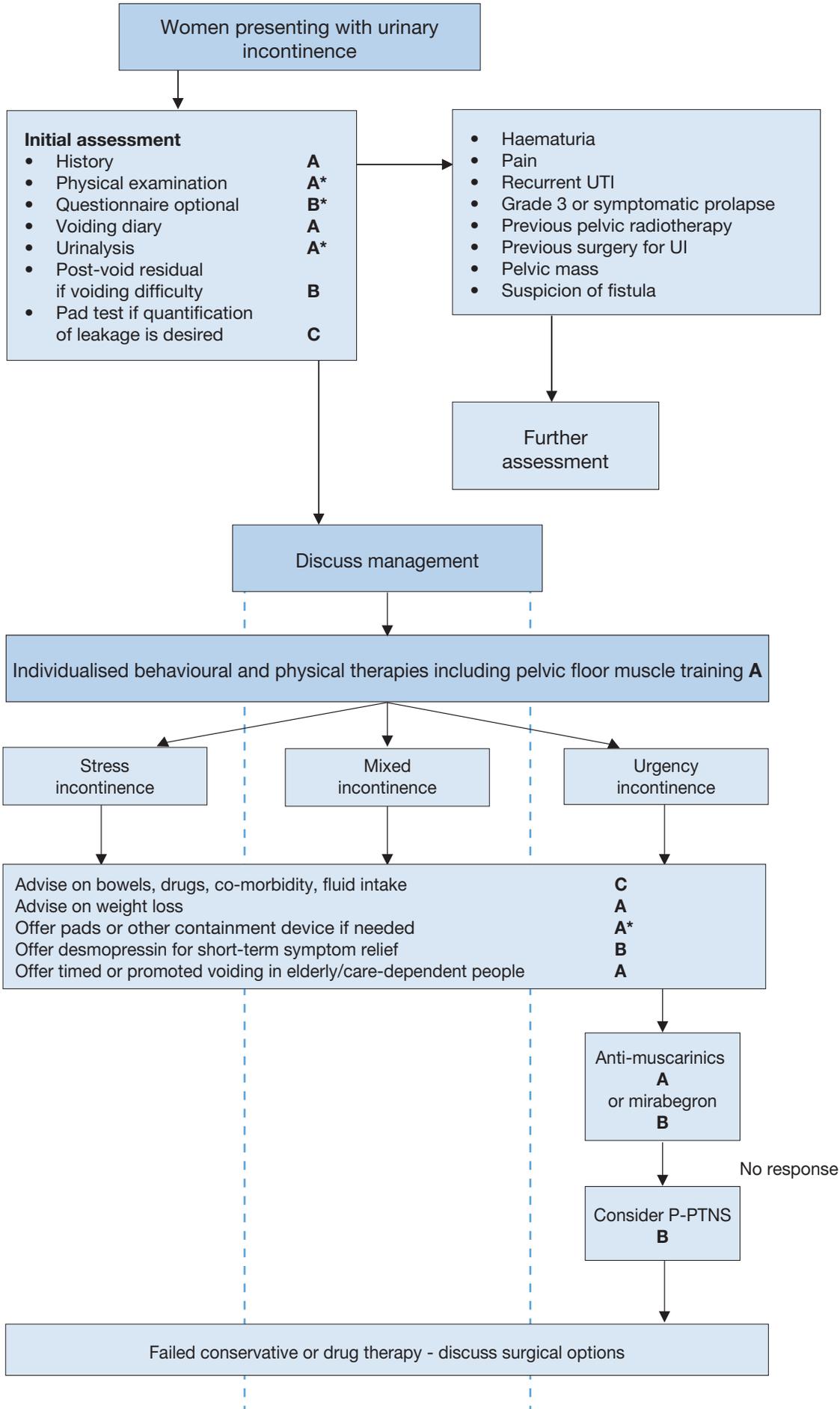
A cohort study of 256 women undergoing inside-out TVT-O reported similar efficacy in older vs. younger women, but there was a higher risk of *de novo* urgency in older patients [327].

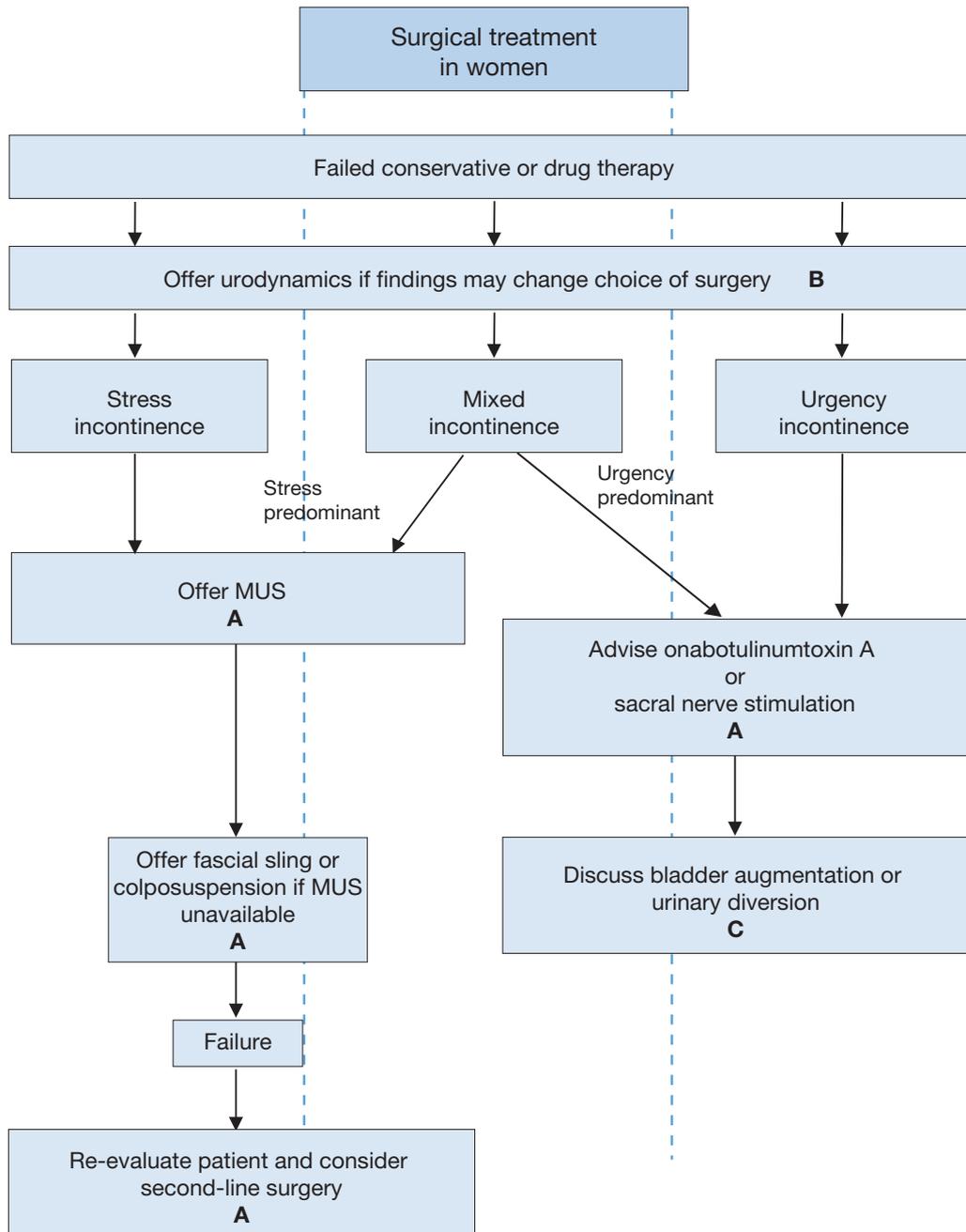
Cohort studies have shown the effectiveness of onabotulinum toxin A injections in the elderly and frail elderly [426, 448], although a comparison of cohort groups suggests that there is a lower success rate in the frail elderly and also a higher rate of increased PVR (> 150 mL) in this group.

Summary of evidence	LE
Older women benefit from surgical treatment for incontinence.	1
The risk of failure from surgical repair of stress urinary incontinence, or of suffering adverse events, appears to increase with age.	2
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4

Recommendation	GR
Inform older women with urinary incontinence about the increased risks associated with surgery (including onabotA injection), together with the lower probability of benefit.	B

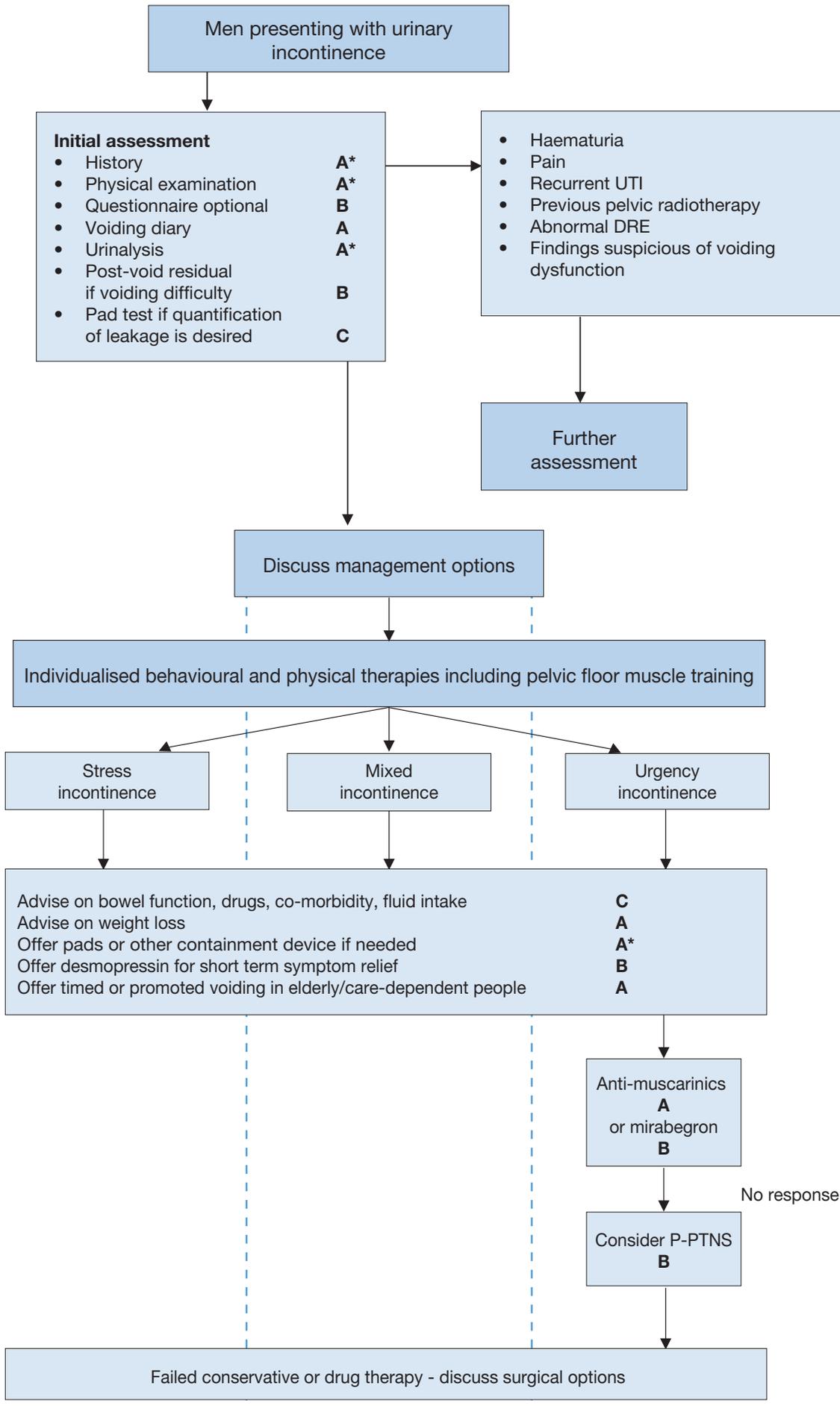
Figure 1: Management and treatment of women presenting with urinary incontinence.

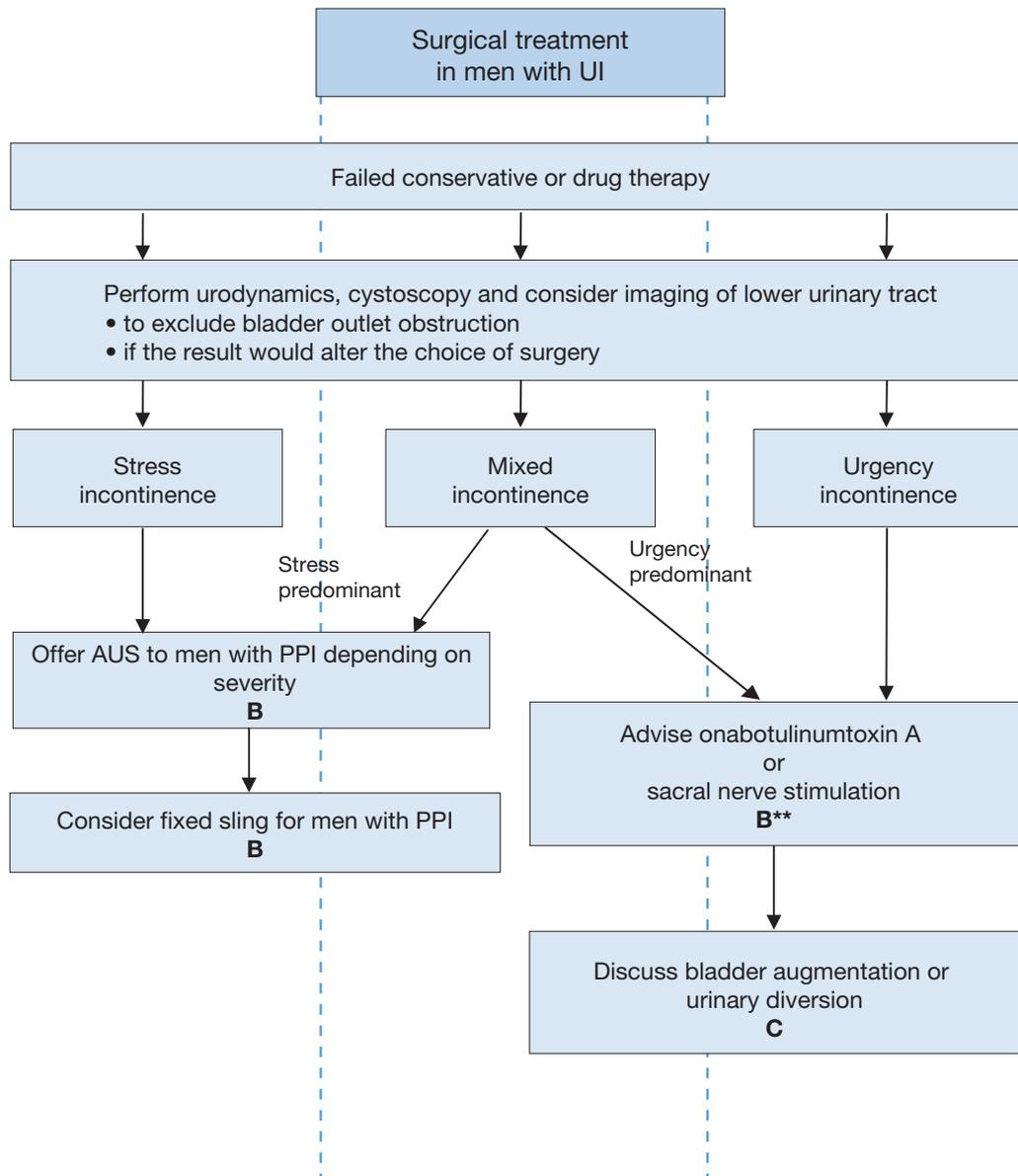




*Based on expert opinion

Figure 2: Management and treatment of men presenting with urinary incontinence.





* Based on expert opinion

** Available evidence on onabotulinumtoxin A and sacral nerve stimulation refers mainly to women.

APPENDIX A: NON OBSTETRIC URINARY FISTULA

A.1 Introduction

The evidence relating to diagnosis and treatment of urinary fistulae is generally poor and this review inevitably relies largely on numerous case series and other consensus statements. In particular, the epidemiology, aetiology, diagnosis, treatment and prevention of non-obstetric fistulae have been described in detail during the recent International Consultations on Incontinence [449, 450]. Most non-obstetric fistulae are iatrogenic in origin, with causes including pelvic surgery (particularly hysterectomy for benign or malignant conditions, caesarean section and obstetric injuries). The risks during pelvic surgery increase relative to the complexity of the resection, the extent of primary disease and when there has been prior radiotherapy (especially for recurrent disease). When a fistula occurs following radiotherapy for primary treatment, this may be an indication of tumour recurrence.

A.2 Diagnosis of fistula

Clinical diagnosis

Leakage of urine is the hallmark sign of a fistula. The leakage is usually painless, may be intermittent if it is position dependent, or may be constant. Unfortunately, intra-operative diagnosis of a GU or GI injury is made in only about half of the cases that result in fistula [451].

The diagnosis of vesicovaginal fistula (VVF) usually requires clinical assessment often in combination with appropriate imaging or laboratory studies. Direct visual inspection, cystoscopy, retrograde bladder filling with a coloured fluid or placement of a tampon into the vagina to identify staining may facilitate the diagnosis of a VVF. A double-dye test to differentiate between a ureterovaginal and VVF may be useful in some cases [452]. Testing the creatinine level in either the extravasated fluid or the accumulated ascites and comparing this to the serum creatinine level will confirm urinary leakage.

Contrast-enhanced CT with late excretory phase reliably diagnoses urinary fistulae and provides information about ureteric integrity and the presence of associated urinoma. Magnetic resonance imaging, in particular with T2 weighting, also provides optimal diagnostic information regarding fistulae and may be preferred for urinary - intestinal fistulae [453].

A.3 Management of vesicovaginal fistula

A.3.1 *Conservative management*

Before epithelialisation is complete an abnormal communication between viscera will tend to close spontaneously, provided that the natural outflow is unobstructed or if urine is diverted. Combining available data gives an overall spontaneous closure rate of 13% ± 23% [2], though this applies largely to small fistulae [450]. Hence, immediate management should be by urinary catheterisation or diversion.

A.3.2 *Surgical management*

Timing of surgery

Findings from uncontrolled case series suggest no difference in success rates for early or delayed closure of VVF.

A.3.2.1 *Surgical approaches*

Vaginal procedures

There are two main types of closure techniques applied to the repair of urinary fistulae, the classical saucerisation/partial colpocleisis [454] and the more commonly used dissection and repair in layers or 'flapsplitting' technique [455]. There are no data comparing their outcomes.

Abdominal procedures

Repair by the abdominal route is indicated when high fistulae are fixed in the vault and are inaccessible through the vagina. A transvesical repair has the advantage of being entirely extraperitoneal. A simple transperitoneal repair is used less often although it is favoured by some using the laparoscopic approach. A combined transperitoneal and transvesical procedure is favoured by many urologists and is particularly useful for fistula repair following Caesarean section. There are no randomised studies comparing abdominal and vaginal approaches. Results of secondary and subsequent repairs are not as good as primary repair [456].

A single RCT compared trimming of the fistula edge with no trimming [457]. There was no difference in success rates but failed repairs in trimmed cases ended up with larger recurrences than untrimmed cases, which were smaller.

Laparoscopic and Robotic

Very small series (single figures) have been reported using these techniques, but whilst laparoscopic repair is feasible with and without robotic assistance, it is not possible to compare outcomes with alternative surgical approaches.

Tissue Interposition

Tissue flaps are often added as an additional layer of repair during VVF surgery. Most commonly, such flaps are utilised in the setting of recurrence after a prior attempt at repair, for VVF related to previous radiotherapy (described later), ischemic or obstetrical fistulae, large fistulae, and finally those associated with a difficult or tenuous closure due to poor tissue quality. However, there is no high-level evidence that the use of such flaps improves outcomes for either complicated or uncomplicated VVF.

Post-operative management

There is no high-level evidence to support any particular practice in post-operative management but most reported series used catheter drainage for at least ten days and longer periods in radiation-associated fistulae (up to three weeks).

A.4 Management of radiation fistula

Modified surgical techniques are often required, and indeed, where the same techniques have been applied to both surgical and post-radiation fistulae, the results from the latter have been consistently poorer [458]. Due to the wide field abnormality surrounding many radiotherapy-associated fistulae, approaches include, on the one hand, permanent urinary and/or faecal diversion [459, 460] or alternatively preliminary urinary and faecal diversion, with later undiversion in selected cases following reconstruction. This may in some cases extend life perhaps inappropriately, and where life expectancy is deemed to be very short, ureteric occlusion might be more appropriate.

A.5 Management of ureteric fistula*General principles*

Patients at higher risk of ureteric injury require experienced surgeons who can identify and protect the ureter and its blood supply to prevent injury and also recognise injury promptly when it occurs. Immediate repair of any intra-operative injury should be performed observing the principles of debridement, adequate blood supply and tension free anastomosis with internal drainage using stents [461]. Delayed presentation of upper tract injury should be suspected in patients whose recovery after relevant abdominal or pelvic surgery is slower than expected, if there is any fluid leak, and if there is any unexpected dilatation of the pelvicalyceal system. Whilst there is no evidence to support the use of one surgical approach over another, there is consensus that repair should adhere to the standard principles of tissue repair and safe anastomosis, and be undertaken by an experienced team. Conservative management is possible with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< two weeks) or delayed (> three months) surgical repair when required [462]. Functional and anatomical imaging should be used to follow up patients after repair to guard against development of ureteric stricture and deterioration in renal function.

Ureterovaginal fistula

Ureterovaginal fistula occurring in the early post-operative phase predominantly after hysterectomy is the most frequent presentation of upper urinary tract fistulae in urological practice. An RCT in 3,141 women undergoing open or laparoscopic gynaecological surgery found that prophylactic insertion of ureteric stents made no difference to the low risk (1%) of ureteric injury [463].

Endoscopic management is sometimes possible [464] by retrograde stenting, percutaneous nephrostomy and antegrade stenting if there is pelvicalyceal dilatation, or ureteroscopic realignment [465].

If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is standard and may require end-to-end anastomosis, re-implantation into the bladder using psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration.

A.6 Management of urethrovaginal fistula*Aetiology*

Whilst they are rare, most urethrovaginal fistulae in adults have an iatrogenic aetiology. Causes include surgical treatment of stress incontinence with bulking agents or synthetic slings, surgery for urethral diverticulum and genital reconstruction in adults. Irradiation and even conservative treatment of prolapse with pessaries can lead to the formation of fistulae.

A.6.1 **Diagnosis**

Clinical vaginal examination, including the three swab test, is often sufficient to diagnose the presence of a urethrovaginal fistula. Urethroscopy and cystoscopy can be performed to assess the extent and location of the fistulae. In cases of difficult diagnosis, voiding cystourethrography (VCUG) or ultrasound can be useful. 3D MRI or CT scan is becoming utilised more widely to clarify anatomy [466, 467].

A.6.2 **Surgical repair**

Choice of surgery will depend on the size, localisation and aetiology of the fistula and the amount of tissue loss. Principles of reconstruction include identifying the fistula, creation of a plane between vaginal wall and urethra, watertight closure of urethral wall, eventual interposition of tissue, and closure of the vaginal wall.

A.6.2.1 *Vaginal approach*

Goodwin described in his series that a vaginal approach yielded a success rate of 70% at first attempt and 92% at second attempt, but that an abdominal approach only leads to a successful closure in 58% of cases. A vaginal approach required less operating time, had less blood loss and a shorter hospitalisation time.

Most authors describe surgical principles that are identical to those of vesicovaginal fistula repair: primary closure rates of 53-95.4% have been described. Pushkar *et al.* described a series of 71 women, treated for urethrovaginal fistula. 90.1% of fistulae were closed at the first vaginal intervention. Additionally, 7.4% were closed during a second vaginal intervention. Despite successful closure, stress incontinence developed in 52%. The stress incontinent patients were treated with synthetic or autologous slings and nearly 60% became dry and an additional 32% improved. Urethral obstruction occurred in 5.6% and was managed by urethral dilation or urethrotomy [468].

Flaps and neourethra.

The simplest flap is a vaginal advancement flap to cover the urethral suture line. Labial tissue can be harvested as a pedicled skin flap. This labial skin can be used as a patch to cover the urethral defect, but can also be used to create a tubular neo-urethra [469, 470]. The construction of a neo-urethra has mostly been described in traumatic aetiologies. In some cases a transpubic approach has been used [471]. The numbers of patients reported are small and there are no data on the long-term outcome of fistula closure and continence rates. The underlying bulbocavernosus tissue can be incorporated in the pedicled flap and probably offers a better vascularisation and more bulking to the repair. This could allow a safer placement of a sling afterwards, in those cases where bothersome stress incontinence would occur post-operatively [472, 473].

Martius flap

While in obstetrical fistula repair it was not found to have any benefit, in a large retrospective study in 440 women the labial bulbocavernosus muscle/fat flap by Martius is still considered by some to be an important adjunctive measure in the treatment of genitourinary fistulae where additional bulking with well vascularised tissue is needed [474]. The series of non-obstetrical aetiology are small and all of them are retrospective. There are no prospective data, nor randomised studies [475]. The indications for Martius flap in the repair of all types of fistulae remain unclear.

Rectus muscle flap

Rectus abdominis muscle flaps have been described by some authors [476, 477].

A.6.2.2 *Abdominal approach*

A retropubic retrourethral technique has been described by Koriatim [478]. This approach allows a urethrovesical flap tube to be fashioned to form a continent neo-urethra.

Summary of evidence	LE
Spontaneous closure of surgical fistulae does occur, although it is not possible to establish the rate with any certainty.	3
There is no evidence that the timing of repair makes a difference to the chances of successful closure of a fistula.	3
There is no high-quality evidence of differing success rates for repair of vesicovaginal fistulae data by vaginal, abdominal, transvesical and transperitoneal approaches.	3
A period of continuous bladder drainage is crucial to successful fistula repair but there is no high-level evidence to support one regime over another.	3
A variety of interpositional grafts can be used in either abdominal or vaginal procedures, although there is little evidence to support their use in any specific setting.	3
Post-radiation fistula	
Successful repair of irradiated fistulae requires prior urinary diversion and the use of non-irradiated tissues to effect repair.	3
Ureteric fistula	
Prophylactic ureteric stent insertion does not reduce risk of ureteric injury during gynaecological surgery.	2
Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase.	4
Urethrovaginal fistula	
Urethrovaginal fistula repair may be complicated by stress incontinence, urethral stricture and urethral shortening necessitating long-term follow-up.	3

Recommendations	GR
General	
Surgeons undertaking complex pelvic surgery should be competent at identifying, preserving and repairing the ureter.	C
Do not routinely use ureteric stents as prophylaxis against injury during routine gynaecological surgery.	B
Suspect ureteric injury or fistula in patients following pelvic surgery if a fluid leak or pelvicalyceal dilatation occurs post-operatively or if drainage fluid contains high levels of creatinine.	C
Suspect uretero-arterial fistula in patients presenting with haematuria with a history of relevant surgery.	C
Use three dimensional imaging techniques to diagnose and localise urinary fistulae.	C
Manage upper urinary tract fistulae by conservative or endoluminal technique where such expertise and facilities exists.	B
Surgical principles	
Surgeons involved in fistula surgery should have appropriate training, skills, and experience to select an appropriate procedure for each patient.	C
Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to and following fistula repair.	C
If a vesicovaginal fistula is diagnosed within six weeks of surgery, consider indwelling catheterisation for a period of up to twelve weeks after the causative event.	C
Tailor the timing of fistula repair to the individual patient and surgeon requirements once any oedema, inflammation, tissue necrosis, or infection, are resolved.	B
Where concurrent ureteric re-implantation or augmentation cystoplasty are required, the abdominal approach is necessary.	C
Ensure that the bladder is continuously drained following fistula repair until healing is confirmed (expert opinion suggests: 10-14 days for simple and/or postsurgical fistulae; 14-21 days for complex and/or post-radiation fistulae).	C
Where urinary and/or faecal diversions are required, avoid using irradiated tissue for repair.	C
Use interposition grafts when repair of radiation associated fistulae is undertaken.	C
In patients with intractable urinary incontinence from radiation-associated fistula, where life expectancy is very short, consider performing ureteric occlusion.	C
Repair persistent ureterovaginal fistula by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence.	C
Consider palliation by nephrostomy tube diversion and endoluminal distal ureteric occlusion for patients with ureteric fistula associated with advanced pelvic cancer and poor performance status.	C
Urethrovaginal fistulae should preferably be repaired by a vaginal approach.	C

5. REFERENCES

1. Abrams, P., *et al.* 5th International Consultation on Incontinence, Paris, February 2012.
2. Stöhrer, M., *et al.* EAU guidelines on neurogenic lower urinary tract dysfunction. *Eur Urol*, 2009. 56: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/19403235>
3. Tekgül, S., *et al.*, EAU Guidelines on Paediatric Urology, in EAU Guidelines. 2017, EAU Guidelines Office: Arnhem, the Netherlands.
4. Lucas, M.G., *et al.* EAU guidelines on assessment and nonsurgical management of urinary incontinence. *Eur Urol*, 2012. 62: 1130.
<https://www.ncbi.nlm.nih.gov/pubmed/22985745>
5. Lucas, M.G., *et al.* EAU guidelines on surgical treatment of urinary incontinence. *Eur Urol*, 2012. 62: 1118.
<https://www.ncbi.nlm.nih.gov/pubmed/23040204>
6. Bedretdinova, D., *et al.* What is the best treatment for nocturia or nocturnal incontinence in terms of improving symptom severity and quality of life?. PROSPERO International prospective register of systematic reviews. 2015.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027092
7. Higgins, J., *et al.* Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2016.
<http://training.cochrane.org/handbook>
8. U.S. Department of Health and Human Services, F.a.D.A. Guidance for Industry - Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009. 2016.
<http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>
9. Farrell, S.A., *et al.* Women's ability to assess their urinary incontinence type using the QUID as an educational tool. *Int Urogynecol J*, 2013. 24: 759.
<https://www.ncbi.nlm.nih.gov/pubmed/22940842>
10. Hess, R., *et al.* Long-term efficacy and safety of questionnaire-based initiation of urgency urinary incontinence treatment. *Am J Obstet Gynecol*, 2013. 209: 244 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/23659987>
11. Reis, R.B., *et al.* Lack of association between the ICIQ-SF questionnaire and the urodynamic diagnosis in men with post radical prostatectomy incontinence. *Acta Cir Bras*, 2013. 28 Suppl 1: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/23381822>
12. Chan, S.S., *et al.* Responsiveness of the Pelvic Floor Distress Inventory and Pelvic Floor Impact Questionnaire in women undergoing treatment for pelvic floor disorders. *Int Urogynecol J*, 2013. 24: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/22669425>
13. Kim, J., *et al.* 1576 Is there a relationship between incontinence impact questionnaire 7 score after surgery for stress urinary incontinence and patient-perceived satisfaction and improvement? *J Urol*. 189: e647.
[http://www.jurology.com/article/S0022-5347\(13\)03402-2/abstract](http://www.jurology.com/article/S0022-5347(13)03402-2/abstract)
14. Tran, M.G., *et al.* Patient reported outcome measures in male incontinence surgery. *Ann R Coll Surg Engl*, 2014. 96: 521.
<https://www.ncbi.nlm.nih.gov/pubmed/25245731>
15. Shy, M., *et al.* Objective Evaluation of Overactive Bladder: Which Surveys Should I Use? *Curr Bladder Dysfunct Rep*, 2013. 8: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/23439804>
16. Abrams, P., *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*, 2002. 21: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/11857671>
17. Haylen, B.T., *et al.* An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. *Neurourol Urodyn*, 2011. 30: 2.
<https://www.ncbi.nlm.nih.gov/pubmed/21181958>
18. Brown, J.S., *et al.* Measurement characteristics of a voiding diary for use by men and women with overactive bladder. *Urology*, 2003. 61: 802.
<https://www.ncbi.nlm.nih.gov/pubmed/12670569>

19. Nygaard, I., *et al.* Reproducibility of the seven-day voiding diary in women with stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*, 2000. 11: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/10738929>
20. Ertberg, P., *et al.* A comparison of three methods to evaluate maximum bladder capacity: cystometry, uroflowmetry and a 24-h voiding diary in women with urinary incontinence. *Acta Obstet Gynecol Scand*, 2003. 82: 374.
<https://www.ncbi.nlm.nih.gov/pubmed/12716323>
21. Fitzgerald, M.P., *et al.* Variability of 24-hour voiding diary variables among asymptomatic women. *J Urol*, 2003. 169: 207.
<https://www.ncbi.nlm.nih.gov/pubmed/12478137>
22. Burgio, K.L., *et al.* Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. *JAMA*, 1998. 280: 1995.
<https://www.ncbi.nlm.nih.gov/pubmed/21224456>
23. Fayyad, A.M., *et al.* Urine production and bladder diary measurements in women with type 2 diabetes mellitus and their relation to lower urinary tract symptoms and voiding dysfunction. *Neurourol Urodyn*, 2010. 29: 354.
<https://www.ncbi.nlm.nih.gov/pubmed/19760759>
24. Homma, Y., *et al.* Assessment of overactive bladder symptoms: comparison of 3-day bladder diary and the overactive bladder symptoms score. *Urology*, 2011. 77: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/20951412>
25. Stav, K., *et al.* Women overestimate daytime urinary frequency: the importance of the bladder diary. *J Urol*, 2009. 181: 2176.
<https://www.ncbi.nlm.nih.gov/pubmed/19296975>
26. van Brummen, H.J., *et al.* The association between overactive bladder symptoms and objective parameters from bladder diary and filling cystometry. *Neurourol Urodyn*, 2004. 23: 38.
<https://www.ncbi.nlm.nih.gov/pubmed/14694455>
27. Gravas, S., *et al.*, EAU Guidelines on the management of Non-Neurogenice Male LUTS, in EAU Guidelines. Edn. published at the 32nd EAU Annual Congress, London, 2017, EAU Guidelines Office Arnhem, The Netherlands.
28. Buchsbaum, G.M., *et al.* Utility of urine reagent strip in screening women with incontinence for urinary tract infection. *Int Urogynecol J Pelvic Floor Dysfunct*, 2004. 15: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/15278254>
29. Arinzon, Z., *et al.* Clinical presentation of urinary tract infection (UTI) differs with aging in women. *Arch Gerontol Geriatr*, 2012. 55: 145.
<https://www.ncbi.nlm.nih.gov/pubmed/>
30. Moore, E.E., *et al.* Urinary incontinence and urinary tract infection: temporal relationships in postmenopausal women. *Obstet Gynecol*, 2008. 111: 317.
<https://www.ncbi.nlm.nih.gov/pubmed/21963175>
31. Ouslander, J.G., *et al.* Does eradicating bacteriuria affect the severity of chronic urinary incontinence in nursing home residents? *Ann Intern Med*, 1995. 122: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/7717597>
32. Goode, P.S., *et al.* Measurement of postvoid residual urine with portable transabdominal bladder ultrasound scanner and urethral catheterization. *Int Urogynecol J Pelvic Floor Dysfunct*, 2000. 11: 296.
<https://www.ncbi.nlm.nih.gov/pubmed/11052565>
33. Griffiths, D.J., *et al.* Variability of post-void residual urine volume in the elderly. *Urol Res*, 1996. 24: 23.
<https://www.ncbi.nlm.nih.gov/pubmed/8966837>
34. Marks, L.S., *et al.* Three-dimensional ultrasound device for rapid determination of bladder volume. *Urology*, 1997. 50: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/9301695>
35. Nygaard, I.E. Postvoid residual volume cannot be accurately estimated by bimanual examination. *Int Urogynecol J Pelvic Floor Dysfunct*, 1996. 7: 74.
<https://www.ncbi.nlm.nih.gov/pubmed/8798090>
36. Ouslander, J.G., *et al.* Use of a portable ultrasound device to measure post-void residual volume among incontinent nursing home residents. *J Am Geriatr Soc*, 1994. 42: 1189.
<https://www.ncbi.nlm.nih.gov/pubmed/7963206>
37. Stoller, M.L., *et al.* The accuracy of a catheterized residual urine. *J Urol*, 1989. 141: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/2908944>

38. Gehrich, A., *et al.* Establishing a mean postvoid residual volume in asymptomatic perimenopausal and postmenopausal women. *Obstet Gynecol*, 2007. 110: 827.
<https://www.ncbi.nlm.nih.gov/pubmed/17906016>
39. Tseng, L.H., *et al.* Postvoid residual urine in women with stress incontinence. *Neurourol Urodyn*, 2008. 27: 48.
<https://www.ncbi.nlm.nih.gov/pubmed/17563112>
40. Haylen, B.T., *et al.* Immediate postvoid residual volumes in women with symptoms of pelvic floor dysfunction. *Obstet Gynecol*, 2008. 111: 1305.
<https://www.ncbi.nlm.nih.gov/pubmed/18515513>
41. Lukacz, E.S., *et al.* Elevated postvoid residual in women with pelvic floor disorders: prevalence and associated risk factors. *Int Urogynecol J Pelvic Floor Dysfunct*, 2007. 18: 397.
<https://www.ncbi.nlm.nih.gov/pubmed/16804634>
42. Milleman, M., *et al.* Post-void residual urine volume in women with overactive bladder symptoms. *J Urol*, 2004. 172: 1911.
<https://www.ncbi.nlm.nih.gov/pubmed/15540753>
43. Brostrom, S., *et al.* Short-term reproducibility of cystometry and pressure-flow micturition studies in healthy women. *Neurourol Urodyn*, 2002. 21: 457.
<https://www.ncbi.nlm.nih.gov/pubmed/12232880>
44. Broekhuis, S.R., *et al.* Reproducibility of same session repeated cystometry and pressure-flow studies in women with symptoms of urinary incontinence. *Neurourol Urodyn*, 2010. 29: 428.
<https://www.ncbi.nlm.nih.gov/pubmed/19618451>
45. Schick, E., *et al.* Predictive value of maximum urethral closure pressure, urethral hypermobility and urethral incompetence in the diagnosis of clinically significant female genuine stress incontinence. *J Urol*, 2004. 171: 1871.
<https://www.ncbi.nlm.nih.gov/pubmed/15076296>
46. Dorflinger, A., *et al.* Urethral pressure profile: is it affected by position? *Neurourol Urodyn*, 2002. 21: 553.
<https://www.ncbi.nlm.nih.gov/pubmed/12382246>
47. Wang, A.C., *et al.* A comparison of urethral pressure profilometry using microtip and double-lumen perfusion catheters in women with genuine stress incontinence. *BJOG*, 2002. 109: 322.
<https://www.ncbi.nlm.nih.gov/pubmed/11950188>
48. Zehnder, P., *et al.* Air charged and microtip catheters cannot be used interchangeably for urethral pressure measurement: a prospective, single-blind, randomized trial. *J Urol*, 2008. 180: 1013.
<https://www.ncbi.nlm.nih.gov/pubmed/18639301>
49. Albo, M.E., *et al.* Burch colposuspension versus fascial sling to reduce urinary stress incontinence. *N Engl J Med*, 2007. 356: 2143.
<https://www.ncbi.nlm.nih.gov/pubmed/17517855>
50. Urinary incontinence in women: management [CG171]. 2013, National Institute for Health and Care Excellence: <https://www.nice.org.uk/guidance/cg171?unlid=79956624201691465614>
51. van Leijsen, S.A., *et al.* The correlation between clinical and urodynamic diagnosis in classifying the type of urinary incontinence in women. A systematic review of the literature. *Neurourol Urodyn*, 2011. 30: 495.
<https://www.ncbi.nlm.nih.gov/pubmed/21298721>
52. Rosier, P., *et al.*, Committee 6: Urodynamic Testing, in: 5th International Consultation on Incontinence, Paris February, 2012, P. Abrams, L. Cardozo, S. Khoury & A. Wein, Editors. 2013: Paris, France.
53. Klarskov, N. Urethral pressure reflectometry. A method for simultaneous measurements of pressure and cross-sectional area in the female urethra. *Dan Med J*, 2012. 59: B4412.
<https://www.ncbi.nlm.nih.gov/pubmed/22381095>
54. Dokmeci, F., *et al.* Comparison of ambulatory versus conventional urodynamics in females with urinary incontinence. *Neurourol Urodyn*, 2010. 29: 518.
<https://www.ncbi.nlm.nih.gov/pubmed/19731314>
55. Radley, S.C., *et al.* Conventional and ambulatory urodynamic findings in women with symptoms suggestive of bladder overactivity. *J Urol*, 2001. 166: 2253.
<https://www.ncbi.nlm.nih.gov/pubmed/11696746>
56. Glazener, C.M., *et al.* Urodynamic studies for management of urinary incontinence in children and adults. *Cochrane Database Syst Rev*, 2012. 1: CD003195.
<https://www.ncbi.nlm.nih.gov/pubmed/22258952>

57. Nitti, V.W., *et al.* Response to fesoterodine in patients with an overactive bladder and urgency urinary incontinence is independent of the urodynamic finding of detrusor overactivity. *BJU Int*, 2010. 105: 1268.
<https://www.ncbi.nlm.nih.gov/pubmed/19889062>
58. Rovner, E., *et al.* Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourol Urodyn*, 2011. 30: 556.
<https://www.ncbi.nlm.nih.gov/pubmed/21351127>
59. Sirls, L.T., *et al.* The effect of urodynamic testing on clinical diagnosis, treatment plan and outcomes in women undergoing stress urinary incontinence surgery. *J Urol*, 2013. 189: 204.
<https://www.ncbi.nlm.nih.gov/pubmed/22982425>
60. Nager, C.W., *et al.* A randomized trial of urodynamic testing before stress-incontinence surgery. *N Engl J Med*, 2012. 366: 1987.
<https://www.ncbi.nlm.nih.gov/pubmed/22551104>
61. van Leijsen, S.A., *et al.* Can preoperative urodynamic investigation be omitted in women with stress urinary incontinence? A non-inferiority randomized controlled trial. *Neurourol Urodyn*, 2012. 31: 1118.
<https://www.ncbi.nlm.nih.gov/pubmed/22488817>
62. van Leijsen, S.A., *et al.* Value of urodynamics before stress urinary incontinence surgery: a randomized controlled trial. *Obstet Gynecol*, 2013. 121: 999.
<https://www.ncbi.nlm.nih.gov/pubmed/23635736>
63. Nager, C.W., *et al.* Baseline urodynamic predictors of treatment failure 1 year after mid urethral sling surgery. *J Urol*, 2011. 186: 597.
<https://www.ncbi.nlm.nih.gov/pubmed/21683412>
64. Dawson, T., *et al.* Factors predictive of post-TVT voiding dysfunction. *Int Urogynecol J Pelvic Floor Dysfunct*, 2007. 18: 1297.
<https://www.ncbi.nlm.nih.gov/pubmed/17347790>
65. Hong, B., *et al.* Factors predictive of urinary retention after a tension-free vaginal tape procedure for female stress urinary incontinence. *J Urol*, 2003. 170: 852.
<https://www.ncbi.nlm.nih.gov/pubmed/12913715>
66. Abdel-Fattah, M., *et al.* Pelvicol pubovaginal sling versus tension-free vaginal tape for treatment of urodynamic stress incontinence: a prospective randomized three-year follow-up study. *Eur Urol*, 2004. 46: 629.
<https://www.ncbi.nlm.nih.gov/pubmed/15474274>
67. Lemack, G.E., *et al.* Normal preoperative urodynamic testing does not predict voiding dysfunction after Burch colposuspension versus pubovaginal sling. *J Urol*, 2008. 180: 2076.
<https://www.ncbi.nlm.nih.gov/pubmed/18804239>
68. Gomha, M.A., *et al.* Artificial urinary sphincter for post-prostatectomy incontinence in men who had prior radiotherapy: a risk and outcome analysis. *J Urol*, 2002. 167: 591.
<https://www.ncbi.nlm.nih.gov/pubmed/11792924>
69. Thiel, D.D., *et al.* Do clinical or urodynamic parameters predict artificial urinary sphincter outcome in post-radical prostatectomy incontinence? *Urology*, 2007. 69: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/17320671>
70. Al Afaa, T., *et al.* Normal lower urinary tract assessment in women: I. Uroflowmetry and post-void residual, pad tests, and bladder diaries. *Int Urogynecol J*, 2012. 23: 681.
<https://www.ncbi.nlm.nih.gov/pubmed/21935667>
71. Krhut, J., *et al.* Pad weight testing in the evaluation of urinary incontinence. *Neurourol Urodyn*, 2014. 33: 507.
<https://www.ncbi.nlm.nih.gov/pubmed/23797972>
72. Painter, V., *et al.* Does patient activity level affect 24-hr pad test results in stress-incontinent women? *Neurourol Urodyn*, 2012. 31: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/21780173>
73. Rimstad, L., *et al.* Pad stress tests with increasing load for the diagnosis of stress urinary incontinence. *Neurourol Urodyn*, 2014. 33: 1135.
<https://www.ncbi.nlm.nih.gov/pubmed/23913797>
74. Richter, H.E., *et al.* Demographic and clinical predictors of treatment failure one year after midurethral sling surgery. *Obstet Gynecol*, 2011. 117: 913.
<https://www.ncbi.nlm.nih.gov/pubmed/21422865>

75. Sato, Y., *et al.* Simple and reliable predictor of urinary continence after radical prostatectomy: serial measurement of urine loss ratio after catheter removal. *Int J Urol*, 2014. 21: 647.
<https://www.ncbi.nlm.nih.gov/pubmed/24612261>
76. Ward, K.L., *et al.* A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up. *Am J Obstet Gynecol*, 2004. 190: 324.
<https://www.ncbi.nlm.nih.gov/pubmed/14981369>
77. Lewicky-Gaupp, C., *et al.* "The cough game": are there characteristic urethrovesical movement patterns associated with stress incontinence? *Int Urogynecol J Pelvic Floor Dysfunct*, 2009. 20: 171.
<https://www.ncbi.nlm.nih.gov/pubmed/18850057>
78. Shek, K.L., *et al.* The effect of childbirth on urethral mobility: a prospective observational study. *J Urol*, 2010. 184: 629.
<https://www.ncbi.nlm.nih.gov/pubmed/20639028>
79. Woodfield, C.A., *et al.* Imaging pelvic floor disorders: trend toward comprehensive MRI. *AJR Am J Roentgenol*, 2010. 194: 1640.
<https://www.ncbi.nlm.nih.gov/pubmed/20489108>
80. Lockhart, M.E., *et al.* Reproducibility of dynamic MR imaging pelvic measurements: a multi-institutional study. *Radiology*, 2008. 249: 534.
<https://www.ncbi.nlm.nih.gov/pubmed/18796659>
81. Shek, K.L., *et al.* The urethral motion profile before and after suburethral sling placement. *J Urol*, 2010. 183: 1450.
<https://www.ncbi.nlm.nih.gov/pubmed/20171657>
82. Chantarasorn, V., *et al.* Sonographic appearance of transobturator slings: implications for function and dysfunction. *Int Urogynecol J*, 2011. 22: 493.
<https://www.ncbi.nlm.nih.gov/pubmed/20967418>
83. Morgan, D.M., *et al.* Urethral sphincter morphology and function with and without stress incontinence. *J Urol*, 2009. 182: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/19450822>
84. Digesu, G.A., *et al.* Three-dimensional ultrasound of the urethral sphincter predicts continence surgery outcome. *Neurourol Urodyn*, 2009. 28: 90.
<https://www.ncbi.nlm.nih.gov/pubmed/18726938>
85. Nguyen, L., *et al.* Surgical technique to overcome anatomical shortcoming: balancing post-prostatectomy continence outcomes of urethral sphincter lengths on preoperative magnetic resonance imaging. *J Urol*, 2008. 179: 1907.
<https://www.ncbi.nlm.nih.gov/pubmed/18353395>
86. Paparel, P., *et al.* Recovery of urinary continence after radical prostatectomy: association with urethral length and urethral fibrosis measured by preoperative and postoperative endorectal magnetic resonance imaging. *Eur Urol*, 2009. 55: 629.
<https://www.ncbi.nlm.nih.gov/pubmed/18801612>
87. Antunes-Lopes, T., *et al.* Biomarkers in lower urinary tract symptoms/overactive bladder: a critical overview. *Curr Opin Urol*, 2014. 24: 352.
<https://www.ncbi.nlm.nih.gov/pubmed/24841379>
88. Sarma, A.V., *et al.* Risk factors for urinary incontinence among women with type 1 diabetes: findings from the epidemiology of diabetes interventions and complications study. *Urology*, 2009. 73: 1203.
<https://www.ncbi.nlm.nih.gov/pubmed/19362350>
89. Coyne, K.S., *et al.* The prevalence of lower urinary tract symptoms (LUTS) and overactive bladder (OAB) by racial/ethnic group and age: results from OAB-POLL. *Neurourol Urodyn*, 2013. 32: 230.
<https://www.ncbi.nlm.nih.gov/pubmed/22847394>
90. Diokno, A.C., *et al.* Medical correlates of urinary incontinence in the elderly. *Urology*, 1990. 36: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/2385880>
91. Alling Moller, L., *et al.* Risk factors for lower urinary tract symptoms in women 40 to 60 years of age. *Obstet Gynecol*, 2000. 96: 446.
<https://www.ncbi.nlm.nih.gov/pubmed/10960640>
92. Byles, J., *et al.* Living with urinary incontinence: a longitudinal study of older women. *Age Ageing*, 2009. 38: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/19258398>
93. Kaplan, S.A., *et al.* Systematic review of the relationship between bladder and bowel function: implications for patient management. *Int J Clin Pract*, 2013. 67: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/23409689>

94. Schnelle, J.F., *et al.* A controlled trial of an intervention to improve urinary and fecal incontinence and constipation. *J Am Geriatr Soc*, 2010. 58: 1504.
<https://www.ncbi.nlm.nih.gov/pubmed/20653804>
95. Geng, V., *et al.*, Catheterisation Indwelling catheters in adults – Urethral and Suprapubic - Evidence-based Guidelines for Best Practice in Urological Health Care. 2012 ed, ed. E.A.o.U. Nurses. 2012, <http://nurses.uroweb.org/guideline/catheterisation-indwelling-catheters-in-adults-urethral-and-suprapubic/>.
96. Geng, V., *et al.*, Male external catheters in adults – Urinary catheter management - Evidence-based Guidelines for Best Practice in Urological Health Care, ed. E.A.o.U. Nurses. Vol. Edn. presented at the 17th International EAUN Meeting, Munich. 2016. 2016, Arnhem, The Netherlands
97. Vahr, S., *et al.*, Catheterisation Urethral Intermittent in adults - Evidence-based Guidelines for Best Practice in Urological Health Care, ed. E.A.o.U. Nurses. Vol. Edn. presented at the 14th International EAUN Meeting, Milan. 2013, Arnhem, The Netherlands
98. McMurdo, M.E., *et al.* A cost-effectiveness study of the management of intractable urinary incontinence by urinary catheterisation or incontinence pads. *J Epidemiol Community Health*, 1992. 46: 222.
<https://www.ncbi.nlm.nih.gov/pubmed/1645076>
99. Saint, S., *et al.* Condom versus indwelling urinary catheters: a randomized trial. *J Am Geriatr Soc*, 2006. 54: 1055.
<https://www.ncbi.nlm.nih.gov/pubmed/16866675>
100. Chartier-Kastler, E., *et al.* Randomized, crossover study evaluating patient preference and the impact on quality of life of urisheaths vs absorbent products in incontinent men. *BJU Int*, 2011. 108: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/20950307>
101. Brazzelli, M., *et al.* Absorbent products for containing urinary and/or fecal incontinence in adults. *J Wound Ostomy Continence Nurs*, 2002. 29: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/11810074>
102. Fader, M., *et al.* A multi-centre evaluation of absorbent products for men with light urinary incontinence. *Neurourol Urodyn*, 2006. 25: 689.
<https://www.ncbi.nlm.nih.gov/pubmed/17009303>
103. Fader, M., *et al.* Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product designs. *Health Technol Assess*, 2008. 12: iii.
<https://www.ncbi.nlm.nih.gov/pubmed/18547500>
104. Jahn, P., *et al.* Types of indwelling urinary catheters for long-term bladder drainage in adults. *Cochrane Database Syst Rev*, 2012. 10: CD004997.
<https://www.ncbi.nlm.nih.gov/pubmed/23076911>
105. Hunter, K.F., *et al.* Long-term bladder drainage: Suprapubic catheter versus other methods: a scoping review. *Neurourol Urodyn*, 2013. 32: 944.
<https://www.ncbi.nlm.nih.gov/pubmed/23192860>
106. Prieto, J., *et al.* Catheter designs, techniques and strategies for intermittent catheterisation: What is the evidence for preventing symptomatic UTI and other complications? A Cochrane systematic review. *Eur Urol Suppl*, 2014. 13: e762.
<http://lib.ajau.ac.ir/booklist/1-s2.0-S156990561460751X-main.pdf>
107. Hakansson, M.A. Reuse versus single-use catheters for intermittent catheterization: what is safe and preferred? Review of current status. *Spinal Cord*, 2014. 52: 511.
<https://www.ncbi.nlm.nih.gov/pubmed/24861702>
108. Hagen, S., *et al.* Washout policies in long-term indwelling urinary catheterisation in adults. *Cochrane Database Syst Rev*, 2010: CD004012.
<https://www.ncbi.nlm.nih.gov/pubmed/20238325>
109. Niel-Weise, B.S., *et al.* Urinary catheter policies for long-term bladder drainage. *Cochrane Database Syst Rev*, 2012: CD004201.
<https://www.ncbi.nlm.nih.gov/pubmed/22895939>
110. Moore, K.N., *et al.* Assessing comfort, safety, and patient satisfaction with three commonly used penile compression devices. *Urology*, 2004. 63: 150.
<https://www.ncbi.nlm.nih.gov/pubmed/14751370>
111. Lipp, A., *et al.* Mechanical devices for urinary incontinence in women. *Cochrane Database Syst Rev*, 2014: CD001756.
<https://www.ncbi.nlm.nih.gov/pubmed/25517397>

112. Hannestad, Y.S., *et al.* Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. *BJOG*, 2003. 110: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/12628262>
113. Arya, L.A., *et al.* Dietary caffeine intake and the risk for detrusor instability: a case-control study. *Obstet Gynecol*, 2000. 96: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/10862848>
114. Bryant, C.M., *et al.* Caffeine reduction education to improve urinary symptoms. *Br J Nurs*, 2002. 11: 560.
<https://www.ncbi.nlm.nih.gov/pubmed/11979209>
115. Swithinbank, L., *et al.* The effect of fluid intake on urinary symptoms in women. *J Urol*, 2005. 174: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/15947624>
116. Tomlinson, B.U., *et al.* Dietary caffeine, fluid intake and urinary incontinence in older rural women. *Int Urogynecol J Pelvic Floor Dysfunct*, 1999. 10: 22.
<https://www.ncbi.nlm.nih.gov/pubmed/10207763>
117. Townsend, M.K., *et al.* Caffeine intake and risk of urinary incontinence progression among women. *Obstet Gynecol*, 2012. 119: 950.
<https://www.ncbi.nlm.nih.gov/pubmed/22525905>
118. Jorgensen, S., *et al.* Heavy lifting at work and risk of genital prolapse and herniated lumbar disc in assistant nurses. *Occup Med (Lond)*, 1994. 44: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/>
119. Nygaard, I., *et al.* Exercise and incontinence. *Obstet Gynecol*, 1990. 75: 848.
<https://www.ncbi.nlm.nih.gov/pubmed/2325968>
120. Nygaard, I.E., *et al.* Urinary incontinence in elite nulliparous athletes. *Obstet Gynecol*, 1994. 84: 183.
<https://www.ncbi.nlm.nih.gov/pubmed/8041527>
121. Bo, K., *et al.* Prevalence of stress and urge urinary incontinence in elite athletes and controls. *Med Sci Sports Exerc*, 2001. 33: 1797.
<https://www.ncbi.nlm.nih.gov/pubmed/11689727>
122. Bo, K., *et al.* Are former female elite athletes more likely to experience urinary incontinence later in life than non-athletes? *Scand J Med Sci Sports*, 2010. 20: 100.
<https://www.ncbi.nlm.nih.gov/pubmed/19000097>
123. Bovell, K., *et al.* Prevalence of stress urinary incontinence among physically active and sedentary female students. *Scand J Med Sci Sports*, 1989. 11: 113.
https://www.researchgate.net/publication/279889192_Prevalence_of_stress_urinary_incontinence_among_physically_active_and_sedentary_female_students
124. Caylet, N., *et al.* Prevalence and occurrence of stress urinary incontinence in elite women athletes. *Can J Urol*, 2006. 13: 3174.
<https://www.ncbi.nlm.nih.gov/pubmed/16953954>
125. Kruger, J.A., *et al.* Pelvic floor function in elite nulliparous athletes. *Ultrasound Obstet Gynecol*, 2007. 30: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/17497753>
126. Thyssen, H.H., *et al.* Urinary incontinence in elite female athletes and dancers. *Int Urogynecol J Pelvic Floor Dysfunct*, 2002. 13: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/11999199>
127. Brown, W.J., *et al.* Too wet to exercise? Leaking urine as a barrier to physical activity in women. *J Sci Med Sport*, 2001. 4: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/11905931>
128. Nygaard, I.E. Does prolonged high-impact activity contribute to later urinary incontinence? A retrospective cohort study of female Olympians. *Obstet Gynecol*, 1997. 90: 718.
<https://www.ncbi.nlm.nih.gov/pubmed/9351751>
129. Eliasson, K., *et al.* Influence of physical activity on urinary leakage in primiparous women. *Scand J Med Sci Sports*, 2005. 15: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/15773862>
130. Kikuchi, A., *et al.* Association between physical activity and urinary incontinence in a community-based elderly population aged 70 years and over. *Eur Urol*, 2007. 52: 868.
<https://www.ncbi.nlm.nih.gov/pubmed/17412488>
131. Kim, H., *et al.* Effectiveness of multidimensional exercises for the treatment of stress urinary incontinence in elderly community-dwelling Japanese women: a randomized, controlled, crossover trial. *J Am Geriatr Soc*, 2007. 55: 1932.
<https://www.ncbi.nlm.nih.gov/pubmed/17944890>

132. Kim, H., *et al.* The effects of multidimensional exercise treatment on community-dwelling elderly Japanese women with stress, urge, and mixed urinary incontinence: a randomized controlled trial. *Int J Nurs Stud*, 2011. 48: 1165.
<https://www.ncbi.nlm.nih.gov/pubmed/21459381>
133. Dowd, T.T., *et al.* Fluid intake and urinary incontinence in older community-dwelling women. *J Community Health Nurs*, 1996. 13: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/8916607>
134. Hashim, H., *et al.* How should patients with an overactive bladder manipulate their fluid intake? *BJU Int*, 2008. 102: 62.
<https://www.ncbi.nlm.nih.gov/pubmed/18284414>
135. Zimmern, P., *et al.* Effect of fluid management on fluid intake and urge incontinence in a trial for overactive bladder in women. *BJU Int*, 2010. 105: 1680.
<https://www.ncbi.nlm.nih.gov/pubmed/19912207>
136. Hunskaar, S. A systematic review of overweight and obesity as risk factors and targets for clinical intervention for urinary incontinence in women. *Neurourol Urodyn*, 2008. 27: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/18951445>
137. Subak, L.L., *et al.* Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med*, 2009. 360: 481.
<https://www.ncbi.nlm.nih.gov/pubmed/11999205>
138. Nygaard, I., *et al.* Prevalence of symptomatic pelvic floor disorders in US women. *JAMA*, 2008. 300: 1311.
<https://www.ncbi.nlm.nih.gov/pubmed/18799443>
139. Chen, C.C., *et al.* Obesity is associated with increased prevalence and severity of pelvic floor disorders in women considering bariatric surgery. *Surg Obes Relat Dis*, 2009. 5: 411.
<https://www.ncbi.nlm.nih.gov/pubmed/19136310>
140. Gozukara, Y.M., *et al.* The improvement in pelvic floor symptoms with weight loss in obese women does not correlate with the changes in pelvic anatomy. *Int Urogynecol J*, 2014. 25: 1219.
<https://www.ncbi.nlm.nih.gov/pubmed/24711149>
141. Brown, J.S., *et al.* Lifestyle intervention is associated with lower prevalence of urinary incontinence: the Diabetes Prevention Program. *Diabetes Care*, 2006. 29: 385.
<https://www.ncbi.nlm.nih.gov/pubmed/16443892>
142. Bump, R.C., *et al.* Obesity and lower urinary tract function in women: effect of surgically induced weight loss. *Am J Obstet Gynecol*, 1992. 167: 392.
<https://www.ncbi.nlm.nih.gov/pubmed/1497041>
143. Subak, L.L., *et al.* Does weight loss improve incontinence in moderately obese women? *Int Urogynecol J Pelvic Floor Dysfunct*, 2002. 13: 40.
<https://www.ncbi.nlm.nih.gov/pubmed/11999205>
144. Wing, R.R., *et al.* Improving urinary incontinence in overweight and obese women through modest weight loss. *Obstet Gynecol*, 2010. 116: 284.
<https://www.ncbi.nlm.nih.gov/pubmed/20664387>
145. Phelan, S., *et al.* Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. *J Urol*, 2012. 187: 939.
<https://www.ncbi.nlm.nih.gov/pubmed/22264468>
146. Burgio, K.L., *et al.* Changes in urinary and fecal incontinence symptoms with weight loss surgery in morbidly obese women. *Obstet Gynecol*, 2007. 110: 1034.
<https://www.ncbi.nlm.nih.gov/pubmed/17978117>
147. Deitel, M., *et al.* Gynecologic-obstetric changes after loss of massive excess weight following bariatric surgery. *J Am Coll Nutr*, 1988. 7: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/3361039>
148. Laungani, R.G., *et al.* Effect of laparoscopic gastric bypass surgery on urinary incontinence in morbidly obese women. *Surg Obes Relat Dis*, 2009. 5: 334.
<https://www.ncbi.nlm.nih.gov/pubmed/19342304>
149. Mishra, G.D., *et al.* Body weight through adult life and risk of urinary incontinence in middle-aged women: results from a British prospective cohort. *Int J Obes (Lond)*, 2008. 32: 1415.
<https://www.ncbi.nlm.nih.gov/pubmed/18626483>
150. Richter, H.E., *et al.* The impact of obesity on urinary incontinence symptoms, severity, urodynamic characteristics and quality of life. *J Urol*, 2010. 183: 622.
<https://www.ncbi.nlm.nih.gov/pubmed/20018326>

151. Danforth, K.N., *et al.* Risk factors for urinary incontinence among middle-aged women. *Am J Obstet Gynecol*, 2006. 194: 339.
<https://www.ncbi.nlm.nih.gov/pubmed/16458626>
152. Imamura, M., *et al.* Systematic review and economic modelling of the effectiveness and cost-effectiveness of non-surgical treatments for women with stress urinary incontinence. *Health Technol Assess*, 2010. 14: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/20738930>
153. Bo, K., *et al.*, An International Urogynecological Association (IUGA) /International Continence Society (ICS) Joint report on the terminology for the conservative management of pelvic floor dysfunction (in Committee Review). 2015.
<https://www.ics.org/Documents/DocumentsDownload.aspx?DocumentID=2808>.
154. Eustice, S., *et al.* Prompted voiding for the management of urinary incontinence in adults. *Cochrane Database Syst Rev*, 2000: CD002113.
<https://www.ncbi.nlm.nih.gov/pubmed/10796861>
155. Flanagan, L., *et al.* Systematic review of care intervention studies for the management of incontinence and promotion of continence in older people in care homes with urinary incontinence as the primary focus (1966-2010). *Geriatr Gerontol Int*, 2012. 12: 600.
<https://www.ncbi.nlm.nih.gov/pubmed/22672329>
156. Ostaszkiwicz, J., *et al.* Habit retraining for the management of urinary incontinence in adults. *Cochrane Database Syst Rev*, 2004: CD002801.
<https://www.ncbi.nlm.nih.gov/pubmed/15106179>
157. Shamliyan, T., *et al.*, Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness. 2012, IUGA-ICS Conservative Management for Female Pelvic Floor Dysfunction: Rockville (MD).
<https://www.ncbi.nlm.nih.gov/books/NBK92960/>
158. Rai, B.P., *et al.* Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults. *Cochrane Database Syst Rev*, 2012. 12: CD003193.
<https://www.ncbi.nlm.nih.gov/pubmed/23235594>
159. Sherburn, M., *et al.* Incontinence improves in older women after intensive pelvic floor muscle training: an assessor-blinded randomized controlled trial. *Neurourol Urodyn*, 2011. 30: 317.
<https://www.ncbi.nlm.nih.gov/pubmed/21284022>
160. Berghmans, B., *et al.* Efficacy of physical therapeutic modalities in women with proven bladder overactivity. *Eur Urol*, 2002. 41: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/12074773>
161. Dumoulin, C., *et al.* Pelvic floor muscle training versus no treatment for urinary incontinence in women. A Cochrane systematic review. *Eur J Phys Rehabil Med*, 2008. 44: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/18385628>
162. Hay-Smith, E.J., *et al.* Comparisons of approaches to pelvic floor muscle training for urinary incontinence in women. *Cochrane Database Syst Rev*, 2011: CD009508.
<https://www.ncbi.nlm.nih.gov/pubmed/22161451>
163. Bo, K., *et al.* Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. *Obstet Gynecol*, 2005. 105: 999.
<https://www.ncbi.nlm.nih.gov/pubmed/15863536>
164. Herderschee, R., *et al.* Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. *Cochrane Database Syst Rev*, 2011: CD009252.
<https://www.ncbi.nlm.nih.gov/pubmed/21735442>
165. Boyle, R., *et al.* Pelvic floor muscle training for prevention and treatment of urinary and faecal incontinence in antenatal and postnatal women. *Cochrane Database Syst Rev*, 2012. 10: CD007471.
<https://www.ncbi.nlm.nih.gov/pubmed/23076935>
166. Haddow, G., *et al.* Effectiveness of a pelvic floor muscle exercise program on urinary incontinence following childbirth. *Int J Evid Based Healthc*, 2005. 3: 103.
<https://www.ncbi.nlm.nih.gov/pubmed/21631746>
167. McFall, S.L., *et al.* Outcomes of a small group educational intervention for urinary incontinence: health-related quality of life. *J Aging Health*, 2000. 12: 301.
<https://www.ncbi.nlm.nih.gov/pubmed/11067699>
168. Campbell, S.E., *et al.* Conservative management for postprostatectomy urinary incontinence. *Cochrane Database Syst Rev*, 2012. 1: CD001843.
<https://www.ncbi.nlm.nih.gov/pubmed/22258946>

169. Geraerts, I., *et al.* Influence of preoperative and postoperative pelvic floor muscle training (PFMT) compared with postoperative PFMT on urinary incontinence after radical prostatectomy: a randomized controlled trial. *Eur Urol*, 2013. 64: 766.
<https://www.ncbi.nlm.nih.gov/pubmed/23357349>
170. Dubbelman, Y., *et al.* The recovery of urinary continence after radical retropubic prostatectomy: a randomized trial comparing the effect of physiotherapist-guided pelvic floor muscle exercises with guidance by an instruction folder only. *BJU Int*, 2010. 106: 515.
<https://www.ncbi.nlm.nih.gov/pubmed/20201841>
171. Moore, K.N., *et al.* Return to continence after radical retropubic prostatectomy: a randomized trial of verbal and written instructions versus therapist-directed pelvic floor muscle therapy. *Urology*, 2008. 72: 1280.
<https://www.ncbi.nlm.nih.gov/pubmed/18384853>
172. Goode, P.S., *et al.* Behavioral therapy with or without biofeedback and pelvic floor electrical stimulation for persistent postprostatectomy incontinence: a randomized controlled trial. *JAMA*, 2011. 305: 151.
<https://www.ncbi.nlm.nih.gov/pubmed/21224456>
173. Glazener, C., *et al.* Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. *Lancet*, 2011. 378: 328.
<https://www.ncbi.nlm.nih.gov/pubmed/21741700>
174. Berghmans, L.C., *et al.* Conservative treatment of stress urinary incontinence in women: a systematic review of randomized clinical trials. *Br J Urol*, 1998. 82: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/9722751>
175. Berghmans, L.C., *et al.* Conservative treatment of urge urinary incontinence in women: a systematic review of randomized clinical trials. *BJU Int*, 2000. 85: 254.
<https://www.ncbi.nlm.nih.gov/pubmed/10671878>
176. Hartmann, K.E., *et al.* Treatment of overactive bladder in women. *Evid Rep Technol Assess (Full Rep)*, 2009: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/19947666>
177. Berghmans, B., *et al.* Electrical stimulation with non-implanted electrodes for urinary incontinence in men. *Cochrane Database Syst Rev*, 2013: CD001202.
<https://www.ncbi.nlm.nih.gov/pubmed/23740763>
178. Lim, R., *et al.* Efficacy of electromagnetic therapy for urinary incontinence: A systematic review. *Neurourol Urodyn*, 2015. 34: 713.
<https://www.ncbi.nlm.nih.gov/pubmed/25251335>
179. Wallace, P.A., *et al.* Sacral nerve neuromodulation in patients with underlying neurologic disease. *Am J Obstet Gynecol*, 2007. 197: 96 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/17618775>
180. Finazzi-Agro, E., *et al.* Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a placebo effect: a randomized, double-blind, placebo controlled trial. *J Urol*, 2010. 184: 2001.
<https://www.ncbi.nlm.nih.gov/pubmed/20850833>
181. Peters, K.M., *et al.* Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmIT trial. *J Urol*, 2010. 183: 1438.
<https://www.ncbi.nlm.nih.gov/pubmed/20171677>
182. Peters, K.M., *et al.* Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. *J Urol*, 2009. 182: 1055.
<https://www.ncbi.nlm.nih.gov/pubmed/19616802>
183. Peters, K.M., *et al.* Percutaneous tibial nerve stimulation for the long-term treatment of overactive bladder: 3-year results of the STEP study. *J Urol*, 2013. 189: 2194.
<https://www.ncbi.nlm.nih.gov/pubmed/23219541>
184. Schreiner, L., *et al.* Randomized trial of transcutaneous tibial nerve stimulation to treat urge urinary incontinence in older women. *Int Urogynecol J*, 2010. 21: 1065.
<https://www.ncbi.nlm.nih.gov/pubmed/20458465>
185. Nygaard, I.E., *et al.* Efficacy of pelvic floor muscle exercises in women with stress, urge, and mixed urinary incontinence. *Am J Obstet Gynecol*, 1996. 174: 120.
<https://www.ncbi.nlm.nih.gov/pubmed/8571994>

186. Lagro-Janssen, T., *et al.* Long-term effect of treatment of female incontinence in general practice. *Br J Gen Pract*, 1998. 48: 1735.
<https://www.ncbi.nlm.nih.gov/pubmed/10198479>
187. Chapple, C., *et al.* The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis. *Eur Urol*, 2005. 48: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/15885877>
188. Chapple, C.R., *et al.* The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur Urol*, 2008. 54: 543.
<https://www.ncbi.nlm.nih.gov/pubmed/18599186>
189. McDonagh, M.S., *et al.*, in *Drug Class Review: Agents for Overactive Bladder: Final Report Update 4*. 2009: Portland (OR).
190. Shamliyan, T.A., *et al.* Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. *Ann Intern Med*, 2008. 148: 459.
<https://www.ncbi.nlm.nih.gov/pubmed/18268288>
191. Buser, N., *et al.* Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. *Eur Urol*, 2012. 62: 1040.
<https://www.ncbi.nlm.nih.gov/pubmed/22999811>
192. Reynolds, W.S., *et al.* Comparative Effectiveness of Anticholinergic Therapy for Overactive Bladder in Women: A Systematic Review and Meta-analysis. *Obstet Gynecol*, 2015. 125: 1423.
<https://www.ncbi.nlm.nih.gov/pubmed/26000514>
193. Goldfischer, E.R., *et al.* Efficacy and safety of oxybutynin topical gel 3% in patients with urgency and/or mixed urinary incontinence: a randomized, double-blind, placebo-controlled study. *Neurourol Urodyn*, 2015. 34: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/24133005>
194. Chapple, C., *et al.* Superiority of fesoterodine 8 mg vs 4 mg in reducing urgency urinary incontinence episodes in patients with overactive bladder: results of the randomised, double-blind, placebo-controlled EIGHT trial. *BJU Int*, 2014. 114: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/24552358>
195. Kaplan, S.A., *et al.* Efficacy and safety of fesoterodine 8 mg in subjects with overactive bladder after a suboptimal response to tolterodine ER. *Int J Clin Pract*, 2014. 68: 1065.
<https://www.ncbi.nlm.nih.gov/pubmed/24898471>
196. Novara, G., *et al.* A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. *Eur Urol*, 2008. 54: 740.
<https://www.ncbi.nlm.nih.gov/pubmed/18632201>
197. Gacci, M., *et al.* Tolterodine extended release in the treatment of male OAB/storage LUTS: a systematic review. *BMC Urol*, 2014. 14: 84.
<https://www.ncbi.nlm.nih.gov/pubmed/25348235>
198. Madhuvrata, P., *et al.* Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev*, 2012. 1: CD005429.
<https://www.ncbi.nlm.nih.gov/pubmed/22258963>
199. Chapple, C., *et al.* Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. *Eur Urol*, 2007. 52: 1204.
<https://www.ncbi.nlm.nih.gov/pubmed/17651893>
200. Herschorn, S., *et al.* Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. *BJU Int*, 2010. 105: 58.
<https://www.ncbi.nlm.nih.gov/pubmed/20132103>
201. DuBeau, C.E., *et al.* Efficacy and tolerability of fesoterodine versus tolterodine in older and younger subjects with overactive bladder: a post hoc, pooled analysis from two placebo-controlled trials. *Neurourol Urodyn*, 2012. 31: 1258.
<https://www.ncbi.nlm.nih.gov/pubmed/22907761>
202. Goode, P.S., *et al.* Incontinence in older women. *JAMA*, 2010. 303: 2172.
<https://www.ncbi.nlm.nih.gov/pubmed/20516418>
203. Gormley, E.A., *et al.* Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*, 2012. 188: 2455.
<https://www.ncbi.nlm.nih.gov/pubmed/23098785>
204. Burgio, K.L., *et al.* Behavioral versus drug treatment for overactive bladder in men: the Male Overactive Bladder Treatment in Veterans (MOTIVE) Trial. *J Am Geriatr Soc*, 2011. 59: 2209.
<https://www.ncbi.nlm.nih.gov/pubmed/21224456>

205. Mattiasson, A., *et al.* Efficacy of simplified bladder training in patients with overactive bladder receiving a solifenacin flexible-dose regimen: results from a randomized study. *BJU Int*, 2010. 105: 1126.
<https://www.ncbi.nlm.nih.gov/pubmed/19818077>
206. Ayeleke, R.O., *et al.* Pelvic floor muscle training added to another active treatment versus the same active treatment alone for urinary incontinence in women. *Cochrane Database Syst Rev*, 2015: CD010551.
<https://www.ncbi.nlm.nih.gov/pubmed/26526663>
207. Manriquez, V., *et al.* Transcutaneous posterior tibial nerve stimulation versus extended release oxybutynin in overactive bladder patients. A prospective randomized trial. *Eur J Obstet Gynecol Reprod Biol*, 2016. 196: 6.
<https://www.ncbi.nlm.nih.gov/pubmed/26645117>
208. Franzen, K., *et al.* Electrical stimulation compared with tolterodine for treatment of urge/urge incontinence amongst women--a randomized controlled trial. *Int Urogynecol J*, 2010. 21: 1517.
<https://www.ncbi.nlm.nih.gov/pubmed/20585755>
209. Kosilov, K.V., *et al.* Randomized controlled trial of cyclic and continuous therapy with tiroprium and solifenacin combination for severe overactive bladder in elderly patients with regard to patient compliance. *Ther Adv Urol*, 2014. 6: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/25435915>
210. Veenboer, P.W., *et al.* Long-term adherence to antimuscarinic therapy in everyday practice: a systematic review. *J Urol*, 2014. 191: 1003.
<https://www.ncbi.nlm.nih.gov/pubmed/24140548>
211. Sand, P.K., *et al.* Long-term safety, tolerability and efficacy of fesoterodine in subjects with overactive bladder symptoms stratified by age: pooled analysis of two open-label extension studies. *Drugs Aging*, 2012. 29: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/22276958>
212. Scarpero, H., *et al.* Long-term safety, tolerability, and efficacy of fesoterodine treatment in men and women with overactive bladder symptoms. *Curr Med Res Opin*, 2011. 27: 921.
<https://www.ncbi.nlm.nih.gov/pubmed/21355814>
213. D'Souza, A.O., *et al.* Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan. *J Manag Care Pharm*, 2008. 14: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/18439051>
214. Sears, C.L., *et al.* Overactive bladder medication adherence when medication is free to patients. *J Urol*, 2010. 183: 1077.
<https://www.ncbi.nlm.nih.gov/pubmed/20092838>
215. Shaya, F.T., *et al.* Persistence with overactive bladder pharmacotherapy in a Medicaid population. *Am J Manag Care*, 2005. 11: S121.
<https://www.ncbi.nlm.nih.gov/pubmed/16161385>
216. Yeaw, J., *et al.* Comparing adherence and persistence across 6 chronic medication classes. *J Manag Care Pharm*, 2009. 15: 728.
<https://www.ncbi.nlm.nih.gov/pubmed/19954264>
217. Yu, Y.F., *et al.* Persistence and adherence of medications for chronic overactive bladder/urinary incontinence in the california medicaid program. *Value Health*, 2005. 8: 495.
<https://www.ncbi.nlm.nih.gov/pubmed/16091027>
218. Kalder, M., *et al.* Discontinuation of treatment using anticholinergic medications in patients with urinary incontinence. *Obstet Gynecol*, 2014. 124: 794.
<https://www.ncbi.nlm.nih.gov/pubmed/25198276>
219. DuBeau, C.E., *et al.* Incontinence in the frail elderly: report from the 4th International Consultation on Incontinence. *Neurourol Urodyn*, 2010. 29: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/20025027>
220. Fink, H.A., *et al.* Treatment interventions in nursing home residents with urinary incontinence: a systematic review of randomized trials. *Mayo Clin Proc*, 2008. 83: 1332.
<https://www.ncbi.nlm.nih.gov/pubmed/19046552>
221. Ancelin, M.L., *et al.* Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ*, 2006. 332: 455.
<https://www.ncbi.nlm.nih.gov/pubmed/16452102>
222. Tannenbaum, C., *et al.* A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs Aging*, 2012. 29: 639.
<https://www.ncbi.nlm.nih.gov/pubmed/22812538>

223. Gray, S.L., *et al.* Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*, 2015. 175: 401.
<https://www.ncbi.nlm.nih.gov/pubmed/25621434>
224. Risacher, S.L., *et al.* Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol*, 2016. 73: 721.
<http://dx.doi.org/10.1001/jamaneurol.2016.0580>
225. Kessler, T.M., *et al.* Adverse event assessment of antimuscarinics for treating overactive bladder: a network meta-analytic approach. *PLoS One*, 2011. 6: e16718.
<https://www.ncbi.nlm.nih.gov/pubmed/21373193>
226. Paquette, A., *et al.* Systematic review and meta-analysis: do clinical trials testing antimuscarinic agents for overactive bladder adequately measure central nervous system adverse events? *J Am Geriatr Soc*, 2011. 59: 1332.
<https://www.ncbi.nlm.nih.gov/pubmed/21718264>
227. Kay, G., *et al.* Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. *Eur Urol*, 2006. 50: 317.
<https://www.ncbi.nlm.nih.gov/pubmed/16687205>
228. Isik, A.T., *et al.* Tropicium and cognition in patients with late onset Alzheimer disease. *J Nutr Health Aging*, 2009. 13: 672.
<https://www.ncbi.nlm.nih.gov/pubmed/19657549>
229. Lackner, T.E., *et al.* Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence. *J Am Geriatr Soc*, 2008. 56: 862.
<https://www.ncbi.nlm.nih.gov/pubmed/18410326>
230. Lackner, T.E., *et al.* Efficacy of oral extended-release oxybutynin in cognitively impaired older nursing home residents with urge urinary incontinence: a randomized placebo-controlled trial. *J Am Med Dir Assoc*, 2011. 12: 639.
<https://www.ncbi.nlm.nih.gov/pubmed/21450183>
231. Minassian, V.A., *et al.* Randomized trial of oxybutynin extended versus immediate release for women aged 65 and older with overactive bladder: lessons learned from conducting a trial. *J Obstet Gynaecol Can*, 2007. 29: 726.
<https://www.ncbi.nlm.nih.gov/pubmed/17825137>
232. Wagg, A., *et al.* Randomised, multicentre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study. *Eur Urol*, 2013. 64: 74.
<https://www.ncbi.nlm.nih.gov/pubmed/23332882>
233. Wesnes, K.A., *et al.* Exploratory pilot study assessing the risk of cognitive impairment or sedation in the elderly following single doses of solifenacin 10 mg. *Expert Opin Drug Saf*, 2009. 8: 615.
<https://www.ncbi.nlm.nih.gov/pubmed/19747069>
234. Sink, K.M., *et al.* Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes. *J Am Geriatr Soc*, 2008. 56: 847.
<https://www.ncbi.nlm.nih.gov/pubmed/18384584>
235. Wagg, A., *et al.* Efficacy and tolerability of solifenacin in elderly subjects with overactive bladder syndrome: a pooled analysis. *Am J Geriatr Pharmacother*, 2006. 4: 14.
<https://www.ncbi.nlm.nih.gov/pubmed/16730617>
236. Zinner, N., *et al.* Impact of solifenacin on quality of life, medical care use, work productivity, and health utility in the elderly: an exploratory subgroup analysis. *Am J Geriatr Pharmacother*, 2009. 7: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/20129258>
237. Herschorn, S., *et al.* Tolerability of solifenacin and oxybutynin immediate release in older (> 65 years) and younger (<= 65 years) patients with overactive bladder: sub-analysis from a Canadian, randomized, double-blind study. *Curr Med Res Opin*, 2011. 27: 375.
<https://www.ncbi.nlm.nih.gov/pubmed/21175373>
238. Drutz, H.P., *et al.* Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. *Int Urogynecol J Pelvic Floor Dysfunct*, 1999. 10: 283.
<https://www.ncbi.nlm.nih.gov/pubmed/10543335>
239. Michel, M.C., *et al.* Does gender or age affect the efficacy and safety of tolterodine? *J Urol*, 2002. 168: 1027.
<https://www.ncbi.nlm.nih.gov/pubmed/12187215>

240. Millard, R., *et al.* Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. *J Urol*, 1999. 161: 1551.
<https://www.ncbi.nlm.nih.gov/pubmed/10210394>
241. Zinner, N.R., *et al.* Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. *J Am Geriatr Soc*, 2002. 50: 799.
<https://www.ncbi.nlm.nih.gov/pubmed/12028164>
242. Jumadilova, Z., *et al.* Retrospective evaluation of outcomes in patients with overactive bladder receiving tolterodine versus oxybutynin. *Am J Health Syst Pharm*, 2006. 63: 2357.
<https://www.ncbi.nlm.nih.gov/pubmed/17106009>
243. Chapple, C., *et al.* Darifenacin treatment of patients \geq 65 years with overactive bladder: results of a randomized, controlled, 12-week trial. *Curr Med Res Opin*, 2007. 23: 2347.
<https://www.ncbi.nlm.nih.gov/pubmed/17706004>
244. Lipton, R.B., *et al.* Assessment of cognitive function of the elderly population: effects of darifenacin. *J Urol*, 2005. 173: 493.
<https://www.ncbi.nlm.nih.gov/pubmed/15643227>
245. Pietzko, A., *et al.* Influences of trospium chloride and oxybutynin on quantitative EEG in healthy volunteers. *Eur J Clin Pharmacol*, 1994. 47: 337.
<https://www.ncbi.nlm.nih.gov/pubmed/7875185>
246. Todorova, A., *et al.* Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. *J Clin Pharmacol*, 2001. 41: 636.
<https://www.ncbi.nlm.nih.gov/pubmed/11402632>
247. Staskin, D.R., *et al.* Trospium chloride once-daily extended release is effective and well tolerated for the treatment of overactive bladder syndrome: an integrated analysis of two randomised, phase III trials. *Int J Clin Pract*, 2009. 63: 1715.
<https://www.ncbi.nlm.nih.gov/pubmed/19930332>
248. Sand, P.K., *et al.* Trospium chloride once-daily extended release is efficacious and tolerated in elderly subjects (aged \geq 75 years) with overactive bladder syndrome. *BJU Int*, 2011. 107: 612.
<https://www.ncbi.nlm.nih.gov/pubmed/20707790>
249. Kraus, S.R., *et al.* Efficacy and tolerability of fesoterodine in older and younger subjects with overactive bladder. *Urology*, 2010. 76: 1350.
<https://www.ncbi.nlm.nih.gov/pubmed/20974482>
250. Dubeau, C.E., *et al.* Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo controlled trial. *J Urol*, 2014. 191: 395.
<https://www.ncbi.nlm.nih.gov/pubmed/23973522>
251. Mariappan, P., *et al.* Duloxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI) for the treatment of stress urinary incontinence: a systematic review. *Eur Urol*, 2007. 51: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/17014950>
252. Li, J., *et al.* The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. *Int Urol Nephrol*, 2013. 45: 679.
<https://www.ncbi.nlm.nih.gov/pubmed/23504618>
253. Wagg, A., *et al.* Review of the efficacy and safety of fesoterodine for treating overactive bladder and urgency urinary incontinence in elderly patients. *Drugs Aging*, 2015. 32: 103.
<https://www.ncbi.nlm.nih.gov/pubmed/25673122>
254. Wagg, A., *et al.* Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder. *Int J Clin Pract*, 2010. 64: 1279.
<https://www.ncbi.nlm.nih.gov/pubmed/20529135>
255. Wagg, A., *et al.* Long-term safety, tolerability and efficacy of flexible-dose fesoterodine in elderly patients with overactive bladder: open-label extension of the SOFIA trial. *Neurourol Urodyn*, 2014. 33: 106.
<https://www.ncbi.nlm.nih.gov/pubmed/23460503>
256. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*, 2015. 63: 2227.
<https://www.ncbi.nlm.nih.gov/pubmed/26446832>
257. Boustani, M., *et al.* Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*, 2008. 4: 311.
<http://dx.doi.org/10.2217/1745509X.4.3.311>
258. Cai, X., *et al.* Long-term anticholinergic use and the aging brain. *Alzheimers Dement*, 2013. 9: 377.
<https://www.ncbi.nlm.nih.gov/pubmed/23183138>

259. Campbell, N., *et al.* The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging*, 2009. 4: 225.
<https://www.ncbi.nlm.nih.gov/pubmed/19554093>
260. Carriere, I., *et al.* Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Arch Intern Med*, 2009. 169: 1317.
<https://www.ncbi.nlm.nih.gov/pubmed/19636034>
261. Fox, C., *et al.* Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc*, 2011. 59: 1477.
<https://www.ncbi.nlm.nih.gov/pubmed/21707557>
262. Chapple, C.R., *et al.* Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. *NeuroUrol Urodyn*, 2014. 33: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/24127366>
263. Cui, Y., *et al.* The efficacy and safety of mirabegron in treating OAB: a systematic review and meta-analysis of phase III trials. *Int Urol Nephrol*, 2014. 46: 275.
<https://www.ncbi.nlm.nih.gov/pubmed/23896942>
264. Herschorn, S., *et al.* A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the beta(3) adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. *Urology*, 2013. 82: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/23769122>
265. Yamaguchi, O., *et al.* Phase III, randomised, double-blind, placebo-controlled study of the beta3-adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder. *BJU Int*, 2014. 113: 951.
<https://www.ncbi.nlm.nih.gov/pubmed/24471907>
266. Wu, T., *et al.* The role of mirabegron in overactive bladder: a systematic review and meta-analysis. *Urol Int*, 2014. 93: 326.
<https://www.ncbi.nlm.nih.gov/pubmed/25115445>
267. Maman, K., *et al.* Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. *Eur Urol*, 2014. 65: 755.
<https://www.ncbi.nlm.nih.gov/pubmed/24275310>
268. Chapple, C.R., *et al.* Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. *Eur Urol*, 2013. 63: 296.
<https://www.ncbi.nlm.nih.gov/pubmed/23195283>
269. Castro-Diaz, D., *et al.* The effect of mirabegron on patient-related outcomes in patients with overactive bladder: the results of post hoc correlation and responder analyses using pooled data from three randomized Phase III trials. *Qual Life Res*, 2015. 24: 1719.
<https://www.ncbi.nlm.nih.gov/pubmed/25688038>
270. Chapple, C., *et al.* Efficacy of the beta3-adrenoceptor agonist mirabegron for the treatment of overactive bladder by severity of incontinence at baseline: a post hoc analysis of pooled data from three randomised phase 3 trials. *Eur Urol*, 2015. 67: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/25092537>
271. Malik, M., *et al.* Proarrhythmic safety of repeat doses of mirabegron in healthy subjects: a randomized, double-blind, placebo-, and active-controlled thorough QT study. *Clin Pharmacol Ther*, 2012. 92: 696.
<https://www.ncbi.nlm.nih.gov/pubmed/23149929>
272. Martin, N., *et al.* Randomised, double-blind, placebo-controlled study to assess the ocular safety of mirabegron in normotensive IOP research subjects. *Eur Urol Suppl*, 2014. 13: e686. [No abstract available].
273. Wagg, A., *et al.* Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus antimuscarinics in overactive bladder: Early experience in Canada. *Can Urol Assoc J*, 2015. 9: 343.
<https://www.ncbi.nlm.nih.gov/pubmed/26644809>
274. Nitti, V.W., *et al.* Urodynamics and safety of the beta(3)-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. *J Urol*, 2013. 190: 1320.
<https://www.ncbi.nlm.nih.gov/pubmed/23727415>
275. Kelleher, C., *et al.* A post-HOC analysis of pooled data from 3 randomised phase 3 trials of mirabegron in patients with overactive bladder (OAB): Correlations between objective and subjective outcome measures. *Int Urogynecol J Pelvic Floor Dysfunct*, 2013. 24: S119. [No abstract available].

276. MacDiarmid, S., *et al.* Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy. *J Urol*, 2016. 196: 809.
<https://www.ncbi.nlm.nih.gov/pubmed/27063854>
277. Ghoniem, G.M., *et al.* A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. *J Urol*, 2005. 173: 1647.
<https://www.ncbi.nlm.nih.gov/pubmed/15821528>
278. Bump, R.C., *et al.* Long-term efficacy of duloxetine in women with stress urinary incontinence. *BJU Int*, 2008. 102: 214.
<https://www.ncbi.nlm.nih.gov/pubmed/18422764>
279. Vella, M., *et al.* Duloxetine 1 year on: the long-term outcome of a cohort of women prescribed duloxetine. *Int Urogynecol J Pelvic Floor Dysfunct*, 2008. 19: 961.
<https://www.ncbi.nlm.nih.gov/pubmed/18231697>
280. Cody, J.D., *et al.* Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev*, 2012. 10: CD001405.
<https://www.ncbi.nlm.nih.gov/pubmed/23076892>
281. Lyytinen, H., *et al.* Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol*, 2006. 108: 1354.
<https://www.ncbi.nlm.nih.gov/pubmed/17138766>
282. Yumru, A.E., *et al.* The use of local 17beta-oestradiol treatment for improving vaginal symptoms associated with post-menopausal oestrogen deficiency. *J Int Med Res*, 2009. 37: 198.
<https://www.ncbi.nlm.nih.gov/pubmed/19215691>
283. Robinson, D., *et al.* Estrogens and the lower urinary tract. *Neurourol Urodyn*, 2011. 30: 754.
<https://www.ncbi.nlm.nih.gov/pubmed/21661025>
284. Mettler, L., *et al.* Long-term treatment of atrophic vaginitis with low-dose oestradiol vaginal tablets. *Maturitas*, 1991. 14: 23.
<https://www.ncbi.nlm.nih.gov/pubmed/1791769>
285. Weber, M.A., *et al.* Local Oestrogen for Pelvic Floor Disorders: A Systematic Review. *PLoS One*, 2015. 10: e0136265.
<https://www.ncbi.nlm.nih.gov/pubmed/26383760>
286. Castellani, D., *et al.* Low-Dose Intravaginal Estriol and Pelvic Floor Rehabilitation in Post-Menopausal Stress Urinary Incontinence. *Urol Int*, 2015. 95: 417.
<https://www.ncbi.nlm.nih.gov/pubmed/26043913>
287. Grady, D., *et al.* Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. *Obstet Gynecol*, 2001. 97: 116.
<https://www.ncbi.nlm.nih.gov/pubmed/16260510>
288. Hendrix, S.L., *et al.* Effects of estrogen with and without progestin on urinary incontinence. *JAMA*, 2005. 293: 935.
<https://www.ncbi.nlm.nih.gov/pubmed/15728164>
289. Rossouw, J.E., *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*, 2002. 288: 321.
<https://www.ncbi.nlm.nih.gov/pubmed/12117397>
290. Steinauer, J.E., *et al.* Postmenopausal hormone therapy: does it cause incontinence? *Obstet Gynecol*, 2005. 106: 940.
<https://www.ncbi.nlm.nih.gov/pubmed/16260510>
291. Goldstein, S.R., *et al.* Incidence of urinary incontinence in postmenopausal women treated with raloxifene or estrogen. *Menopause*, 2005. 12: 160.
<https://www.ncbi.nlm.nih.gov/pubmed/15772563>
292. Molander, U., *et al.* Effect of oral oestriol on vaginal flora and cytology and urogenital symptoms in the post-menopause. *Maturitas*, 1990. 12: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/2255263>
293. Samsioe, G., *et al.* Occurrence, nature and treatment of urinary incontinence in a 70-year-old female population. *Maturitas*, 1985. 7: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/3908884>
294. Wang, C.J., *et al.* Low dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: a double-blind, placebo controlled, randomized study. *J Urol*, 2011. 185: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/21074790>

295. Robinson, D., *et al.* Antidiuresis: a new concept in managing female daytime urinary incontinence. *BJU Int*, 2004. 93: 996.
<https://www.ncbi.nlm.nih.gov/pubmed/15142150>
296. Khullar, V., *et al.* Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. *Urology*, 2004. 64: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/15302476>
297. Kreder, K.J., Jr., *et al.* Tolterodine is equally effective in patients with mixed incontinence and those with urge incontinence alone. *BJU Int*, 2003. 92: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/12930432>
298. Kelleher, C., *et al.* Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*, 2006. 17: 382.
<https://www.ncbi.nlm.nih.gov/pubmed/16283422>
299. Staskin, D.R., *et al.* Short- and long-term efficacy of solifenacin treatment in patients with symptoms of mixed urinary incontinence. *BJU Int*, 2006. 97: 1256.
<https://www.ncbi.nlm.nih.gov/pubmed/16686722>
300. Bent, A.E., *et al.* Duloxetine compared with placebo for the treatment of women with mixed urinary incontinence. *Neurourol Urodyn*, 2008. 27: 212.
<https://www.ncbi.nlm.nih.gov/pubmed/17580357>
301. Bump, R.C., *et al.* Mixed urinary incontinence symptoms: urodynamic findings, incontinence severity, and treatment response. *Obstet Gynecol*, 2003. 102: 76.
<https://www.ncbi.nlm.nih.gov/pubmed/12850610>
302. Bai, S.W., *et al.* Comparison of the efficacy of Burch colposuspension, pubovaginal sling, and tension-free vaginal tape for stress urinary incontinence. *Int J Gynaecol Obstet*, 2005. 91: 246.
<https://www.ncbi.nlm.nih.gov/pubmed/16242695>
303. Foote, A.J., *et al.* Laparoscopic colposuspension versus vaginal suburethral slingplasty: a randomised prospective trial. *Aust N Z J Obstet Gynaecol*, 2006. 46: 517.
<https://www.ncbi.nlm.nih.gov/pubmed/17116057>
304. Jelovsek, J.E., *et al.* Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up. *BJOG*, 2008. 115: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/18081602>
305. Liapis, A., *et al.* Burch colposuspension and tension-free vaginal tape in the management of stress urinary incontinence in women. *Eur Urol*, 2002. 41: 469.
<https://www.ncbi.nlm.nih.gov/pubmed/12074820>
306. Paraiso, M.F., *et al.* Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial. *Obstet Gynecol*, 2004. 104: 1249.
<https://www.ncbi.nlm.nih.gov/pubmed/15572485>
307. Persson, J., *et al.* Cost-analyzes based on a prospective, randomized study comparing laparoscopic colposuspension with a tension-free vaginal tape procedure. *Acta Obstet Gynecol Scand*, 2002. 81: 1066.
<https://www.ncbi.nlm.nih.gov/pubmed/12421176>
308. Tellez Martinez-Fornes, M., *et al.* A three year follow-up of a prospective open randomized trial to compare tension-free vaginal tape with Burch colposuspension for treatment of female stress urinary incontinence. *Actas Urol Esp*, 2009. 33: 1088.
<https://www.ncbi.nlm.nih.gov/pubmed/20096179>
309. Ustun, Y., *et al.* Tension-free vaginal tape compared with laparoscopic Burch urethropexy. *J Am Assoc Gynecol Laparosc*, 2003. 10: 386.
<https://www.ncbi.nlm.nih.gov/pubmed/14567818>
310. Valpas, A., *et al.* Tension-free vaginal tape and laparoscopic mesh colposuspension for stress urinary incontinence. *Obstet Gynecol*, 2004. 104: 42.
<https://www.ncbi.nlm.nih.gov/pubmed/15228999>
311. Wang, A.C., *et al.* Comparison of tension-free vaginal taping versus modified Burch colposuspension on urethral obstruction: a randomized controlled trial. *Neurourol Urodyn*, 2003. 22: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/12707868>
312. Ward, K., *et al.* Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ*, 2002. 325: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/12114234>
313. Drahoradova, P., *et al.* Comparative development of quality of life between TVT and Burch colposuspension. *Neurourol Urodyn*, 2004. 23: 278
<http://www.ics.org/Abstracts/Publish/42/000278.pdf>

314. El-Barky, E., *et al.* Tension free vaginal tape versus Burch colposuspension for treatment of female stress urinary incontinence. *Int Urol Nephrol*, 2005. 37: 277.
<https://www.ncbi.nlm.nih.gov/pubmed/16142556>
315. Maher, C., *et al.* Laparoscopic colposuspension or tension-free vaginal tape for recurrent stress urinary incontinence and/or urethral sphincter deficiency-a randomised controlled trial. *Neurourol Urodyn.*, 2004. 23: 433.
<http://www.ics.org/Abstracts/Publish/42/000025.pdf>
316. Ogah, J., *et al.* Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*, 2009: CD006375.
<https://www.ncbi.nlm.nih.gov/pubmed/19821363>
317. Latthe, P.M., *et al.* Two routes of transobturator tape procedures in stress urinary incontinence: a meta-analysis with direct and indirect comparison of randomized trials. *BJU Int*, 2010. 106: 68.
<https://www.ncbi.nlm.nih.gov/pubmed/19912182>
318. Mostafa, A., *et al.* Single-incision mini-slings versus standard midurethral slings in surgical management of female stress urinary incontinence: an updated systematic review and meta-analysis of effectiveness and complications. *Eur Urol*, 2014. 65: 402.
<https://www.ncbi.nlm.nih.gov/pubmed/24055431>
319. Novara, G., *et al.* Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. *Eur Urol*, 2010. 58: 218.
<https://www.ncbi.nlm.nih.gov/pubmed/20434257>
320. Jha, S., *et al.* Impact of incontinence surgery on sexual function: a systematic review and meta-analysis. *J Sex Med*, 2012. 9: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/21699671>
321. De Souza, A., *et al.* Sexual function following retropubic TVT and transobturator Monarc sling in women with intrinsic sphincter deficiency: a multicentre prospective study. *Int Urogynecol J*, 2012. 23: 153.
<https://www.ncbi.nlm.nih.gov/pubmed/21811769>
322. Filocamo, M.T., *et al.* The impact of mid-urethral slings for the treatment of urodynamic stress incontinence on female sexual function: a multicenter prospective study. *J Sex Med*, 2011. 8: 2002.
<https://www.ncbi.nlm.nih.gov/pubmed/21762389>
323. Rechberger, T., *et al.* Body mass index does not influence the outcome of anti-incontinence surgery among women whereas menopausal status and ageing do: a randomised trial. *Int Urogynecol J*, 2010. 21: 801.
<https://www.ncbi.nlm.nih.gov/pubmed/20179903>
324. Barber, M.D., *et al.* Risk factors associated with failure 1 year after retropubic or transobturator midurethral slings. *Am J Obstet Gynecol*, 2008. 199: 666 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/19084098>
325. Richter, H.E., *et al.* Predictors of treatment failure 24 months after surgery for stress urinary incontinence. *J Urol*, 2008. 179: 1024.
<https://www.ncbi.nlm.nih.gov/pubmed/18206917>
326. Campeau, L., *et al.* A multicenter, prospective, randomized clinical trial comparing tension-free vaginal tape surgery and no treatment for the management of stress urinary incontinence in elderly women. *Neurourol Urodyn*, 2007. 26: 990.
<https://www.ncbi.nlm.nih.gov/pubmed/17638307>
327. Groutz, A., *et al.* The safety and efficacy of the "inside-out" trans-obturator TVT in elderly versus younger stress-incontinent women: a prospective study of 353 consecutive patients. *Neurourol Urodyn*, 2011. 30: 380.
<https://www.ncbi.nlm.nih.gov/pubmed/20665549>
328. Dean, N.M., *et al.* Laparoscopic colposuspension for urinary incontinence in women. *Cochrane Database Syst Rev*, 2006: CD002239.
<https://www.ncbi.nlm.nih.gov/pubmed/16855989>
329. Glazener, C.M., *et al.* Anterior vaginal repair for urinary incontinence in women. *Cochrane Database Syst Rev*, 2001: CD001755.
<https://www.ncbi.nlm.nih.gov/pubmed/11279728>
330. Lapitan, M.C., *et al.* Open retropubic colposuspension for urinary incontinence in women. *Cochrane Database Syst Rev*, 2009: CD002912.
<https://www.ncbi.nlm.nih.gov/pubmed/19821297>

331. Rehman, H., *et al.* Traditional suburethral sling operations for urinary incontinence in women. *Cochrane Database Syst Rev*, 2011: CD001754.
<https://www.ncbi.nlm.nih.gov/pubmed/21249648>
332. Keegan, P.E., *et al.* Periurethral injection therapy for urinary incontinence in women. *Cochrane Database Syst Rev*, 2007: CD003881.
<https://www.ncbi.nlm.nih.gov/pubmed/17636740>
333. Kirchin, V., *et al.* Urethral injection therapy for urinary incontinence in women. *Cochrane Database Syst Rev*, 2012: CD003881.
<https://www.ncbi.nlm.nih.gov/pubmed/22336797>
334. Ghoneim, G., *et al.* Systematic review of polydimethylsiloxane injection: Short and long term durability outcomes for female stress urinary incontinence. *Neurourol Urodyn*, 2012. 2: S9. [No abstract available].
335. Kuhn, A., *et al.* Where should bulking agents for female urodynamic stress incontinence be injected? *Int Urogynecol J Pelvic Floor Dysfunct*, 2008. 19: 817.
<https://www.ncbi.nlm.nih.gov/pubmed/18157642>
336. Lightner, D., *et al.* A new injectable bulking agent for treatment of stress urinary incontinence: results of a multicenter, randomized, controlled, double-blind study of Durasphere. *Urology*, 2001. 58: 12.
<https://www.ncbi.nlm.nih.gov/pubmed/11445471>
337. Carr, L.K., *et al.* Autologous muscle derived cell therapy for stress urinary incontinence: a prospective, dose ranging study. *J Urol*, 2013. 189: 595.
<https://www.ncbi.nlm.nih.gov/pubmed/23260547>
338. Maher, C.F., *et al.* Pubovaginal sling versus transurethral Macroplastique for stress urinary incontinence and intrinsic sphincter deficiency: a prospective randomised controlled trial. *BJOG*, 2005. 112: 797.
<https://www.ncbi.nlm.nih.gov/pubmed/15924540>
339. Ashok, K., *et al.* Recurrent urinary stress incontinence: an overview. *J Obstet Gynaecol Res*, 2010. 36: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/20598022>
340. Lovatsis, D., *et al.* Guidelines for the evaluation and treatment of recurrent urinary incontinence following pelvic floor surgery. *J Obstet Gynaecol Can*, 2010. 32: 893.
<https://www.ncbi.nlm.nih.gov/pubmed/21050525>
341. Bakali, E., *et al.* Treatment of recurrent stress urinary incontinence after failed minimally invasive synthetic suburethral tape surgery in women. *Cochrane Database Syst Rev*, 2013: CD009407.
<https://www.ncbi.nlm.nih.gov/pubmed/23450602>
342. Abdel-Fattah, M., *et al.* Evaluation of transobturator tension-free vaginal tapes in management of women with recurrent stress urinary incontinence. *Urology*, 2011. 77: 1070.
<https://www.ncbi.nlm.nih.gov/pubmed/21414653>
343. Richter, H.E., *et al.* Baseline predictors of one year treatment failure of retropubic and transobturator midurethral sling procedures for stress urinary incontinence. *Female Pelvic Med Reconstr Surg* 2010. 16: S62. [No abstract available].
344. Amaye-Obu, F.A., *et al.* Surgical management of recurrent stress urinary incontinence: A 12-year experience. *Am J Obstet Gynecol*, 1999. 181: 1296.
<https://www.ncbi.nlm.nih.gov/pubmed/10601904>
345. Rardin, C.R., *et al.* Tension-free vaginal tape: outcomes among women with primary versus recurrent stress urinary incontinence. *Obstet Gynecol*, 2002. 100: 893.
<https://www.ncbi.nlm.nih.gov/pubmed/12423849>
346. Rezapour, M., *et al.* Tension-Free vaginal tape (TVT) in women with mixed urinary incontinence--a long-term follow-up. *Int Urogynecol J Pelvic Floor Dysfunct*, 2001. 12 Suppl 2: S15.
<https://www.ncbi.nlm.nih.gov/pubmed/11450974>
347. Lee, K.S., *et al.* Outcomes following repeat mid urethral synthetic sling after failure of the initial sling procedure: rediscovery of the tension-free vaginal tape procedure. *J Urol*, 2007. 178: 1370.
<https://www.ncbi.nlm.nih.gov/pubmed/17706716>
348. Stav, K., *et al.* Repeat synthetic mid urethral sling procedure for women with recurrent stress urinary incontinence. *J Urol*, 2010. 183: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/19913831>
349. Jarvis, G.J. Surgery for genuine stress incontinence. *Br J Obstet Gynaecol*, 1994. 101: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/8018606>
350. Shaikh, S., *et al.* Mechanical devices for urinary incontinence in women. *Cochrane Database Syst Rev*, 2006: CD001756.
<https://www.ncbi.nlm.nih.gov/pubmed/16855977>

351. Chung, E., *et al.* 25-year experience in the outcome of artificial urinary sphincter in the treatment of female urinary incontinence. *BJU Int*, 2010. 106: 1664.
<https://www.ncbi.nlm.nih.gov/pubmed/20500509>
352. Costa, P., *et al.* The use of an artificial urinary sphincter in women with type III incontinence and a negative Marshall test. *J Urol*, 2001. 165: 1172.
<https://www.ncbi.nlm.nih.gov/pubmed/11257664>
353. Heitz, M., *et al.* [Therapy of female urinary incontinence with the AMS 800 artificial sphincter. Indications, outcome, complications and risk factors]. *Urologe A*, 1997. 36: 426.
<https://www.ncbi.nlm.nih.gov/pubmed/9424794>
354. Vayleux, B., *et al.* Female urinary incontinence and artificial urinary sphincter: study of efficacy and risk factors for failure and complications. *Eur Urol*, 2011. 59: 1048.
<https://www.ncbi.nlm.nih.gov/pubmed/21420781>
355. Alonso Rodriguez, D., *et al.* Four years experience with the flowsecure artificial urinary sphincter. Problems and solutions. *Neurourol Urodyn* 2011. 30: #250.
<https://www.ics.org/Abstracts/Publish/106/000250.pdf>
356. Mandron, E., *et al.* Laparoscopic artificial urinary sphincter implantation for female genuine stress urinary incontinence: technique and 4-year experience in 25 patients. *BJU Int*, 2010. 106: 1194.
<https://www.ncbi.nlm.nih.gov/pubmed/20132197>
357. Roupret, M., *et al.* Laparoscopic approach for artificial urinary sphincter implantation in women with intrinsic sphincter deficiency incontinence: a single-centre preliminary experience. *Eur Urol*, 2010. 57: 499.
<https://www.ncbi.nlm.nih.gov/pubmed/19346059>
358. Aboseif, S.R., *et al.* The adjustable continence therapy system for recurrent female stress urinary incontinence: 1-year results of the North America Clinical Study Group. *J Urol*, 2009. 181: 2187.
<https://www.ncbi.nlm.nih.gov/pubmed/19296967>
359. Aboseif, S.R., *et al.* Treatment of moderate to severe female stress urinary incontinence with the adjustable continence therapy (ACT) device after failed surgical repair. *World J Urol*, 2011. 29: 249.
<https://www.ncbi.nlm.nih.gov/pubmed/20959993>
360. Kocjancic, E., *et al.* Adjustable continence therapy for severe intrinsic sphincter deficiency and recurrent female stress urinary incontinence: long-term experience. *J Urol*, 2010. 184: 1017.
<https://www.ncbi.nlm.nih.gov/pubmed/18761534>
361. Wachter, J., *et al.* Adjustable continence therapy for female urinary incontinence: a minimally invasive option for difficult cases. *Urol Int*, 2008. 81: 160.
<https://www.ncbi.nlm.nih.gov/pubmed/18758213>
362. Maher, C., *et al.* Surgical management of pelvic organ prolapse in women. *Cochrane Database Syst Rev*, 2013: CD004014.
<https://www.ncbi.nlm.nih.gov/pubmed/23633316>
363. Brubaker, L., *et al.* Two-year outcomes after sacrocolpopexy with and without burch to prevent stress urinary incontinence. *Obstet Gynecol*, 2008. 112: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/18591307>
364. Wei, J.T., *et al.* A midurethral sling to reduce incontinence after vaginal prolapse repair. *N Engl J Med*, 2012. 366: 2358.
<https://www.ncbi.nlm.nih.gov/pubmed/22716974>
365. Borstad, E., *et al.* Surgical strategies for women with pelvic organ prolapse and urinary stress incontinence. *Int Urogynecol J*, 2010. 21: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/19940978>
366. Costantini, E., *et al.* Pelvic organ prolapse repair with and without prophylactic concomitant Burch colposuspension in continent women: a randomized, controlled trial with 8-year followup. *J Urol*, 2011. 185: 2236.
<https://www.ncbi.nlm.nih.gov/pubmed/21497843>
367. Costantini, E., *et al.* Urgency, detrusor overactivity and posterior vault prolapse in women who underwent pelvic organ prolapse repair. *Urol Int*, 2013. 90: 168.
<https://www.ncbi.nlm.nih.gov/pubmed/23327990>
368. Kummeling, M.T., *et al.* Sequential urodynamic assessment before and after laparoscopic sacrocolpopexy. *Acta Obstet Gynecol Scand*, 2013. 92: 172.
<https://www.ncbi.nlm.nih.gov/pubmed/23157606>
369. Lee, D.M., *et al.* A predictive factor in overactive bladder symptoms improvement after combined anterior vaginal wall prolapse repair: a pilot study. *Korean J Urol*, 2012. 53: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/22741049>

370. Visco, A.G., *et al.* The role of preoperative urodynamic testing in stress-continent women undergoing sacrocolpopexy: the Colpopexy and Urinary Reduction Efforts (CARE) randomized surgical trial. *Int Urogynecol J Pelvic Floor Dysfunct*, 2008. 19: 607.
<https://www.ncbi.nlm.nih.gov/pubmed/18185903>
371. Duecy, E.E., *et al.* Urodynamic prediction of occult stress urinary incontinence before vaginal surgery for advanced pelvic organ prolapse: evaluation of postoperative outcomes. *Female Pelvic Med Reconstr Surg*, 2010. 16: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/22453344>
372. Chughtai, B., *et al.* Ambulatory pessary trial unmasks occult stress urinary incontinence. *Obstet Gynecol Int*, 2012. 2012: 392027.
<https://www.ncbi.nlm.nih.gov/pubmed/21949665>
373. Blander, D.S., *et al.* Endoluminal magnetic resonance imaging in the evaluation of urethral diverticula in women. *Urology*, 2001. 57: 660.
<https://www.ncbi.nlm.nih.gov/pubmed/11306374>
374. Pathi, S.D., *et al.* Utility of clinical parameters, cystourethroscopy, and magnetic resonance imaging in the preoperative diagnosis of urethral diverticula. *Int Urogynecol J*, 2013. 24: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/22707007>
375. Dwarkasing, R.S., *et al.* MRI evaluation of urethral diverticula and differential diagnosis in symptomatic women. *AJR Am J Roentgenol*, 2011. 197: 676.
<https://www.ncbi.nlm.nih.gov/pubmed/21862811>
376. Chung, D.E., *et al.* Urethral diverticula in women: discrepancies between magnetic resonance imaging and surgical findings. *J Urol*, 2010. 183: 2265.
<https://www.ncbi.nlm.nih.gov/pubmed/20400161>
377. Han, D.H., *et al.* Outcomes of surgery of female urethral diverticula classified using magnetic resonance imaging. *Eur Urol*, 2007. 51: 1664.
<https://www.ncbi.nlm.nih.gov/pubmed/17335961>
378. Ingber, M.S., *et al.* Surgically corrected urethral diverticula: long-term voiding dysfunction and reoperation rates. *Urology*, 2011. 77: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/20800882>
379. Lee, U.J., *et al.* Rate of de novo stress urinary incontinence after urethral diverticulum repair. *Urology*, 2008. 71: 849.
<https://www.ncbi.nlm.nih.gov/pubmed/18355904>
380. Ljungqvist, L., *et al.* Female urethral diverticulum: 26-year followup of a large series. *J Urol*, 2007. 177: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/17162049>
381. Migliari, R., *et al.* Recurrent pseudodiverticula of female urethra: five-year experience. *Urology*, 2009. 73: 1218.
<https://www.ncbi.nlm.nih.gov/pubmed/19375782>
382. Stav, K., *et al.* Urinary symptoms before and after female urethral diverticulectomy--can we predict de novo stress urinary incontinence? *J Urol*, 2008. 180: 2088.
<https://www.ncbi.nlm.nih.gov/pubmed/18804229>
383. Thomas, A.A., *et al.* Urethral diverticula in 90 female patients: a study with emphasis on neoplastic alterations. *J Urol*, 2008. 180: 2463.
<https://www.ncbi.nlm.nih.gov/pubmed/18930487>
384. Cornu, J.N., *et al.* Duloxetine for mild to moderate postprostatectomy incontinence: preliminary results of a randomised, placebo-controlled trial. *Eur Urol*, 2011. 59: 148.
<https://www.ncbi.nlm.nih.gov/pubmed/21030144>
385. Filocamo, M.T., *et al.* Pharmacologic treatment in postprostatectomy stress urinary incontinence. *Eur Urol*, 2007. 51: 1559.
<https://www.ncbi.nlm.nih.gov/pubmed/16942833>
386. Alan, C., *et al.* Efficacy of Duloxetine in the Early Management of Urinary Continence after Radical Prostatectomy. *Curr Urol*, 2015. 8: 43.
<https://www.ncbi.nlm.nih.gov/pubmed/26195963>
387. Imamoglu, M.A., *et al.* The comparison of artificial urinary sphincter implantation and endourethral macropastique injection for the treatment of postprostatectomy incontinence. *Eur Urol*, 2005. 47: 209.
<https://www.ncbi.nlm.nih.gov/pubmed/15661416>
388. Secin, F.P., *et al.* [Limited efficacy of permanent injectable agents in the treatment of stress urinary incontinence after radical prostatectomy]. *Arch Esp Urol*, 2005. 58: 431.
<https://www.ncbi.nlm.nih.gov/pubmed/16078785>

389. Mantovani, F., *et al.* VID-2.02: Bulkamide hydrogel: limits of a new bulking agent in the mini-invasive therapy of incontinence after prostatectomy. *Urology*. 76: S50.
<http://dx.doi.org/10.1016/j.urology.2010.09.012>
390. Werther, M., *et al.* Stress urinary incontinence after radical prostatectomy: long term effects of endoscopic injection with dextranomer/hyaluronic acid copolymer. *Neurourol Urodyn*, 2009. 8.
<https://www.ics.org/Abstracts/Publish/47/000643.pdf>
391. Silva, L.A., *et al.* Surgery for stress urinary incontinence due to presumed sphincter deficiency after prostate surgery. *Cochrane Database Syst Rev*, 2011: CD008306.
<https://www.ncbi.nlm.nih.gov/pubmed/21491408>
392. Zeif, H.-J., *et al.* The male sling for post-radical prostatectomy urinary incontinence: urethral compression versus urethral relocation or what is next? *Brit J Med Surg Urol*, 2010. 3: 134.
<http://www.sciencedirect.com/science/article/pii/S1875974210000248>
393. Cornel, E.B., *et al.* Can advance transobturator sling suspension cure male urinary postoperative stress incontinence? *J Urol*, 2010. 183: 1459.
<https://www.ncbi.nlm.nih.gov/pubmed/20172561>
394. Abrams, P., *et al.* Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. *Neurourol Urodyn*, 2010. 29: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/20025020>
395. Bauer, R.M., *et al.* Contemporary management of postprostatectomy incontinence. *Eur Urol*, 2011. 59: 985.
<https://www.ncbi.nlm.nih.gov/pubmed/21458914>
396. Herschorn, S., *et al.* Surgical treatment of stress incontinence in men. *Neurourol Urodyn*, 2010. 29: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/20025026>
397. Bauer, R.M., *et al.* Results of the AdVance transobturator male sling after radical prostatectomy and adjuvant radiotherapy. *Urology*, 2011. 77: 474.
<https://www.ncbi.nlm.nih.gov/pubmed/21167563>
398. Bauer, R.M., *et al.* Mid-term results for the retroluminal transobturator sling suspension for stress urinary incontinence after prostatectomy. *BJU Int*, 2011. 108: 94.
<https://www.ncbi.nlm.nih.gov/pubmed/20883489>
399. Cornu, J.N., *et al.* Mid-term evaluation of the transobturator male sling for post-prostatectomy incontinence: focus on prognostic factors. *BJU Int*, 2011. 108: 236.
<https://www.ncbi.nlm.nih.gov/pubmed/20955265>
400. Gill, B.C., *et al.* Patient perceived effectiveness of a new male sling as treatment for post-prostatectomy incontinence. *J Urol*, 2010. 183: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/19913826>
401. Rehder, P., *et al.* The 1 year outcome of the transobturator retroluminal repositioning sling in the treatment of male stress urinary incontinence. *BJU Int*, 2010. 106: 1668.
<https://www.ncbi.nlm.nih.gov/pubmed/20518761>
402. Kim, J. Long term follow-up of readjustable urethral sling procedure (Remeex System) for male stress urinary incontinence. *Neurourol Urodyn*, 2011. 30: #209.
<http://dx.doi.org/10.1002/nau.21134>
403. Bochove-Overgaauw, D.M., *et al.* An adjustable sling for the treatment of all degrees of male stress urinary incontinence: retrospective evaluation of efficacy and complications after a minimal followup of 14 months. *J Urol*, 2011. 185: 1363.
<https://www.ncbi.nlm.nih.gov/pubmed/21334683>
404. Hubner, W.A., *et al.* Adjustable bulbourethral male sling: experience after 101 cases of moderate-to-severe male stress urinary incontinence. *BJU Int*, 2011. 107: 777.
<https://www.ncbi.nlm.nih.gov/pubmed/20964801>
405. Dalpiaz, O., *et al.* Mid-term complications after placement of the male adjustable suburethral sling: a single center experience. *J Urol*, 2011. 186: 604.
<https://www.ncbi.nlm.nih.gov/pubmed/21684559>
406. Hoda, M.R., *et al.* Early results of a European multicentre experience with a new self-anchoring adjustable transobturator system for treatment of stress urinary incontinence in men. *BJU Int*, 2013. 111: 296.
<https://www.ncbi.nlm.nih.gov/pubmed/23186285>
407. Seweryn, J., *et al.* Initial experience and results with a new adjustable transobturator male system for the treatment of stress urinary incontinence. *J Urol*, 2012. 187: 956.
<https://www.ncbi.nlm.nih.gov/pubmed/22264469>

408. Trigo Rocha, F., *et al.* A prospective study evaluating the efficacy of the artificial sphincter AMS 800 for the treatment of postradical prostatectomy urinary incontinence and the correlation between preoperative urodynamic and surgical outcomes. *Urology*, 2008. 71: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/18242371>
409. Lai, H.H., *et al.* Urodynamic testing in evaluation of postradical prostatectomy incontinence before artificial urinary sphincter implantation. *Urology*, 2009. 73: 1264.
<https://www.ncbi.nlm.nih.gov/pubmed/19371935>
410. Aaronson, D.S., *et al.* Transcorporal artificial urinary sphincter placement for incontinence in high-risk patients after treatment of prostate cancer. *Urology*, 2008. 72: 825.
<https://www.ncbi.nlm.nih.gov/pubmed/18752838>
411. Hudak, S.J., *et al.* Impact of 3.5 cm artificial urinary sphincter cuff on primary and revision surgery for male stress urinary incontinence. *J Urol*, 2011. 186: 1962.
<https://www.ncbi.nlm.nih.gov/pubmed/21944140>
412. O'Connor, R.C., *et al.* Long-term follow-up of single versus double cuff artificial urinary sphincter insertion for the treatment of severe postprostatectomy stress urinary incontinence. *Urology*, 2008. 71: 90.
<https://www.ncbi.nlm.nih.gov/pubmed/18242372>
413. Smith, P., *et al.* 1348 Hypercontinence and cuff erosion after artificial sphincter insertion: A comparison of cuff sizes and placement techniques. *J Urol*, 2011. 185: e538.
<http://www.sciencedirect.com/science/article/pii/S0022534711014170>
414. Lentz, A.C., *et al.* Outcomes following artificial sphincter implantation after prior unsuccessful male sling. *J Urol*, 2012. 187: 2149.
<https://www.ncbi.nlm.nih.gov/pubmed/22503016>
415. Roupret, M., *et al.* Management of stress urinary incontinence following prostate surgery with minimally invasive adjustable continence balloon implants: functional results from a single center prospective study. *J Urol*, 2011. 186: 198.
<https://www.ncbi.nlm.nih.gov/pubmed/21575974>
416. Crivellaro, S., *et al.* Adjustable continence therapy (ProACT) and bone anchored male sling: Comparison of two new treatments of post prostatectomy incontinence. *Int J Urol*, 2008. 15: 910.
<https://www.ncbi.nlm.nih.gov/pubmed/18761534>
417. Gilling, P.J., *et al.* An adjustable continence therapy device for treating incontinence after prostatectomy: a minimum 2-year follow-up. *BJU Int*, 2008. 102: 1426.
<https://www.ncbi.nlm.nih.gov/pubmed/18564132>
418. Gregori, A., *et al.* Transrectal ultrasound-guided implantation of Adjustable Continence Therapy (ProACT): surgical technique and clinical results after a mean follow-up of 2 years. *Eur Urol*, 2010. 57: 430.
<https://www.ncbi.nlm.nih.gov/pubmed/19942340>
419. Hubner, W.A., *et al.* Treatment of incontinence after prostatectomy using a new minimally invasive device: adjustable continence therapy. *BJU Int*, 2005. 96: 587.
<https://www.ncbi.nlm.nih.gov/pubmed/16104915>
420. Martens, F.M., *et al.* ProACT for stress urinary incontinence after radical prostatectomy. *Urol Int*, 2009. 82: 394.
<https://www.ncbi.nlm.nih.gov/pubmed/19506404>
421. Kjaer, L., *et al.* Adjustable continence balloons: clinical results of a new minimally invasive treatment for male urinary incontinence. *Scand J Urol Nephrol*, 2012. 46: 196.
<https://www.ncbi.nlm.nih.gov/pubmed/22364390>
422. Duthie, J.B., *et al.* Botulinum toxin injections for adults with overactive bladder syndrome. *Cochrane Database Syst Rev*, 2011: CD005493.
<https://www.ncbi.nlm.nih.gov/pubmed/22161392>
423. Mangera, A., *et al.* Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). *Eur Urol*, 2011. 60: 784.
<https://www.ncbi.nlm.nih.gov/pubmed/21782318>
424. Chapple, C., *et al.* OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. *Eur Urol*, 2013. 64: 249.
<https://www.ncbi.nlm.nih.gov/pubmed/23608668>

425. Nitti, V.W., *et al.* OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. *J Urol*, 2013. 189: 2186.
<https://www.ncbi.nlm.nih.gov/pubmed/23246476>
426. White, W.M., *et al.* Short-term efficacy of botulinum toxin a for refractory overactive bladder in the elderly population. *J Urol*, 2008. 180: 2522.
<https://www.ncbi.nlm.nih.gov/pubmed/18930481>
427. Visco, A.G., *et al.* Anticholinergic therapy vs. onabotulinumtoxinA for urgency urinary incontinence. *N Engl J Med*, 2012. 367: 1803.
<https://www.ncbi.nlm.nih.gov/pubmed/23036134>
428. Herbison, G.P., *et al.* Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults. *Cochrane Database Syst Rev*, 2009: CD004202.
<https://www.ncbi.nlm.nih.gov/pubmed/19370596>
429. Schmidt, R.A., *et al.* Sacral nerve stimulation for treatment of refractory urinary urge incontinence. Sacral Nerve Stimulation Study Group. *J Urol*, 1999. 162: 352.
<https://www.ncbi.nlm.nih.gov/pubmed/10411037>
430. Weil, E.H., *et al.* Sacral root neuromodulation in the treatment of refractory urinary urge incontinence: a prospective randomized clinical trial. *Eur Urol*, 2000. 37: 161.
<https://www.ncbi.nlm.nih.gov/pubmed/10705194>
431. Brazzelli, M., *et al.* Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. *J Urol*, 2006. 175: 835.
<https://www.ncbi.nlm.nih.gov/pubmed/16469561>
432. Groen, J., *et al.* Sacral neuromodulation as treatment for refractory idiopathic urge urinary incontinence: 5-year results of a longitudinal study in 60 women. *J Urol*, 2011. 186: 954.
<https://www.ncbi.nlm.nih.gov/pubmed/21791355>
433. van Kerrebroeck, P.E., *et al.* Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. *J Urol*, 2007. 178: 2029.
<https://www.ncbi.nlm.nih.gov/pubmed/17869298>
434. Groenendijk, P.M., *et al.* Urodynamic evaluation of sacral neuromodulation for urge urinary incontinence. *BJU Int*, 2008. 101: 325.
<https://www.ncbi.nlm.nih.gov/pubmed/18070199>
435. Cody, J.D., *et al.* Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy. *Cochrane Database Syst Rev*, 2012: CD003306.
<https://www.ncbi.nlm.nih.gov/pubmed/22336788>
436. Kockelbergh, R.C., *et al.* Clam enterocystoplasty in general urological practice. *Br J Urol*, 1991. 68: 38.
<https://www.ncbi.nlm.nih.gov/pubmed/1873689>
437. Awad, S.A., *et al.* Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women. *Br J Urol*, 1998. 81: 569.
<https://www.ncbi.nlm.nih.gov/pubmed/9598629>
438. Greenwell, T.J., *et al.* Augmentation cystoplasty. *BJU Int*, 2001. 88: 511.
<https://www.ncbi.nlm.nih.gov/pubmed/11678743>
439. Cartwright, P.C., *et al.* Bladder autoaugmentation: partial detrusor excision to augment the bladder without use of bowel. *J Urol*, 1989. 142: 1050.
<https://www.ncbi.nlm.nih.gov/pubmed/2795729>
440. Leng, W.W., *et al.* Enterocystoplasty or detrusor myectomy? Comparison of indications and outcomes for bladder augmentation. *J Urol*, 1999. 161: 758.
<https://www.ncbi.nlm.nih.gov/pubmed/10022679>
441. ter Meulen, P.H., *et al.* A study on the feasibility of vesicomyotomy in patients with motor urge incontinence. *Eur Urol*, 1997. 32: 166.
<https://www.ncbi.nlm.nih.gov/pubmed/9286647>
442. Juang, C.M., *et al.* Efficacy analysis of trans-obturator tension-free vaginal tape (TVT-O) plus modified Ingelman-Sundberg procedure versus TVT-O alone in the treatment of mixed urinary incontinence: a randomized study. *Eur Urol*, 2007. 51: 1671.
<https://www.ncbi.nlm.nih.gov/pubmed/17254697>
443. Kuo, H.C. Effect of detrusor function on the therapeutic outcome of a suburethral sling procedure using a polypropylene sling for stress urinary incontinence in women. *Scand J Urol Nephrol*, 2007. 41: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/17454953>

444. Colombo, M., *et al.* The Burch colposuspension for women with and without detrusor overactivity. *Br J Obstet Gynaecol*, 1996. 103: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/8630311>
445. Kulseng-Hanssen, S., *et al.* The tension free vaginal tape operation for women with mixed incontinence: Do preoperative variables predict the outcome? *Neurourol Urodyn*, 2007. 26: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/16894616>
446. Kulseng-Hanssen, S., *et al.* Follow-up of TVT operations in 1,113 women with mixed urinary incontinence at 7 and 38 months. *Int Urogynecol J Pelvic Floor Dysfunct*, 2008. 19: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/17891326>
447. Rechberger, T., *et al.* The clinical effectiveness of retropubic (IVS-02) and transobturator (IVS-04) midurethral slings: randomized trial. *Eur Urol*, 2009. 56: 24.
<https://www.ncbi.nlm.nih.gov/pubmed/19285788>
448. Liao, C.H., *et al.* Increased risk of large post-void residual urine and decreased long-term success rate after intravesical onabotulinumtoxinA injection for refractory idiopathic detrusor overactivity. *J Urol*, 2013. 189: 1804.
<https://www.ncbi.nlm.nih.gov/pubmed/23178902>
449. De Ridder, D., *et al.*, Fistula (Committee 18), in: 5th International Consultation on Incontinence, Paris, February 2012, 2013: Paris, France.
450. De Ridder, D., *et al.*, Fistula - Surgical management of obstetric fistula, in: 5th International Consultation on Incontinence, Paris, February 2012, 2013: Paris, France
<https://www.ncbi.nlm.nih.gov/pubmed/>
451. Ostrzenski, A., *et al.* Bladder injury during laparoscopic surgery. *Obstet Gynecol Surv*, 1998. 53: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/9513988>
452. Hadzi-Djokic, J., *et al.* Vesico-vaginal fistula: report of 220 cases. *Int Urol Nephrol*, 2009. 41: 299.
<https://www.ncbi.nlm.nih.gov/pubmed/18810652>
453. Narayanan, P., *et al.* Fistulas in malignant gynecologic disease: etiology, imaging, and management. *Radiographics*, 2009. 29: 1073.
<https://www.ncbi.nlm.nih.gov/pubmed/19605657>
454. Latzko, W. Postoperative vesicovaginal fistulas. *Am J Surg*, 1942. 58: 211.
<http://www.sciencedirect.com/science/article/pii/S0002961042900096>
455. Wall, L.L. Dr. George Hayward (1791-1863): a forgotten pioneer of reconstructive pelvic surgery. *Int Urogynecol J Pelvic Floor Dysfunct*, 2005. 16: 330.
<https://www.ncbi.nlm.nih.gov/pubmed/15976986>
456. Hilton, P., *et al.* Epidemiological and surgical aspects of urogenital fistulae: a review of 25 years' experience in southeast Nigeria. *Int Urogynecol J Pelvic Floor Dysfunct*, 1998. 9: 189.
<https://www.ncbi.nlm.nih.gov/pubmed/9795822>
457. Shaker, H., *et al.* Obstetric vesico-vaginal fistula repair: should we trim the fistula edges? A randomized prospective study. *Neurourol Urodyn*, 2011. 30: 302.
<https://www.ncbi.nlm.nih.gov/pubmed/21308748>
458. Jovanovic, M., *et al.* Efficiency of urinary fistulas surgical treatment. *Eur Urol Suppl*, 2010. 9: S54.
[http://www.europeanurology.com/article/S1569-9056\(10\)61340-1/abstract/](http://www.europeanurology.com/article/S1569-9056(10)61340-1/abstract/)
459. Krause, S., *et al.* Surgery for urologic complications following radiotherapy for gynecologic cancer. *Scand J Urol Nephrol*, 1987. 21: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/3616502>
460. Langkilde, N.C., *et al.* Surgical repair of vesicovaginal fistulae--a ten-year retrospective study. *Scand J Urol Nephrol*, 1999. 33: 100.
<https://www.ncbi.nlm.nih.gov/pubmed/10360449>
461. Lumen, N., *et al.* Review of the current management of lower urinary tract injuries by the EAU Trauma Guidelines Panel. *Eur Urol*, 2015. 67: 925.
<https://www.ncbi.nlm.nih.gov/pubmed/25576009>
462. Brandes, S., *et al.* Diagnosis and management of ureteric injury: an evidence-based analysis. *BJU Int*, 2004. 94: 277.
<https://www.ncbi.nlm.nih.gov/pubmed/15291852>
463. Morton, H.C., *et al.* Urethral injury associated with minimally invasive mid-urethral sling procedures for the treatment of stress urinary incontinence: a case series and systematic literature search. *BJOG*, 2009. 116: 1120.
<https://www.ncbi.nlm.nih.gov/pubmed/19438488>
464. Shaw, M.B., *et al.* The management of bilateral ureteric injury following radical hysterectomy. *Adv Urol*, 2008: 524919.
<https://www.ncbi.nlm.nih.gov/pubmed/18604294>

465. Narang, V., *et al.* Ureterscopy: savior to the gynecologist? Ureterscopic management of post laparoscopic-assisted vaginal hysterectomy ureterovaginal fistulas. *J Minim Invasive Gynecol*, 2007. 14: 345.
<https://www.ncbi.nlm.nih.gov/pubmed/17478367>
466. Abou-El-Ghar, M.E., *et al.* Radiological diagnosis of vesicouterine fistula: role of magnetic resonance imaging. *J Magn Reson Imaging*, 2012. 36: 438.
<https://www.ncbi.nlm.nih.gov/pubmed/22535687>
467. Quiroz, L.H., *et al.* Three-dimensional ultrasound imaging for diagnosis of urethrovaginal fistula. *Int Urogynecol J*, 2010. 21: 1031.
<https://www.ncbi.nlm.nih.gov/pubmed/20069418>
468. Pushkar, D.Y., *et al.* Management of urethrovaginal fistulas. *Eur Urol*, 2006. 50: 1000.
<https://www.ncbi.nlm.nih.gov/pubmed/16945476>
469. Pushkar, D. Editorial comment on: Transpubic access using pedicle tubularized labial urethroplasty for the treatment of female urethral strictures associated with urethrovaginal fistulas secondary to pelvic fracture. *Eur Urol*, 2009. 56: 200.
<https://www.ncbi.nlm.nih.gov/pubmed/18468776>
470. Xu, Y.M., *et al.* Transpubic access using pedicle tubularized labial urethroplasty for the treatment of female urethral strictures associated with urethrovaginal fistulas secondary to pelvic fracture. *Eur Urol*, 2009. 56: 193.
<https://www.ncbi.nlm.nih.gov/pubmed/18468778>
471. Huang, C.R., *et al.* The management of old urethral injury in young girls: analysis of 44 cases. *J Pediatr Surg*, 2003. 38: 1329.
<https://www.ncbi.nlm.nih.gov/pubmed/14523814>
472. Candiani, P., *et al.* Repair of a recurrent urethrovaginal fistula with an island bulbocavernous musculocutaneous flap. *Plast Reconstr Surg*, 1993. 92: 1393.
<https://www.ncbi.nlm.nih.gov/pubmed/8248420>
473. McKinney, D.E. Use of full thickness patch graft in urethrovaginal fistula. *J Urol*, 1979. 122: 416.
<https://www.ncbi.nlm.nih.gov/pubmed/381691>
474. Browning, A. Lack of value of the Martius fibrofatty graft in obstetric fistula repair. *Int J Gynaecol Obstet*, 2006. 93: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/16530766>
475. Baskin, D., *et al.* Martius repair in urethrovaginal defects. *J Pediatr Surg*, 2005. 40: 1489.
<https://www.ncbi.nlm.nih.gov/pubmed/16150356>
476. Atan, A., *et al.* Treatment of refractory urethrovaginal fistula using rectus abdominis muscle flap in a six-year-old girl. *Urology*, 2007. 69: 384 e11.
<https://www.ncbi.nlm.nih.gov/pubmed/17320687>
477. Bruce, R.G., *et al.* Use of rectus abdominis muscle flap for the treatment of complex and refractory urethrovaginal fistulas. *J Urol*, 2000. 163: 1212.
<https://www.ncbi.nlm.nih.gov/pubmed/10737499>
478. Koraitim, M. A new retropubic retrourethral approach for large vesico-urethrovaginal fistulas. *J Urol*, 1985. 134: 1122.
<https://www.ncbi.nlm.nih.gov/pubmed/4057401>

6. CONFLICT OF INTEREST

All members of the Urinary Incontinence Guidelines Panel have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website: <http://uroweb.org/guideline/>. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Neuro-Urology

B. Blok (Co-chair), J. Pannek (Co-chair) D. Castro-Diaz,
G. del Popolo, J. Groen, R. Hamid, G. Karsenty, T.M. Kessler
Guidelines Associates: H. Ecclestone, B. Padilla-Fernández,
L. 't Hoen, S. Musco, V. Phé, S. Reuvers, M.P. Schneider

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Neuro-Urology Guidelines aim to provide information for clinical practitioners on the incidence, definitions, diagnosis, therapy, and follow-up of neuro-urological disorders. These Guidelines reflect the current opinion of experts in this specific pathology and represent a state-of-the-art reference for all clinicians, as of the publication date.

The terminology used and the diagnostic procedures advised throughout these Guidelines follow the recommendations for investigations of the lower urinary tract (LUT) as published by the International Continence Society (ICS) [1-3]. Readers are advised to consult other EAU Guidelines that may address different aspects of the topics discussed in this document.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Neuro-Urology Guidelines Panel consists of an international multidisciplinary group of neuro-urological experts. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guideline/neuro-urology/>.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is also available, both in print and as a mobile application. These are abridged versions which may require consultation with the full text version. A guideline summary has also been published in European Urology [4]. All are available through the EAU website: <http://www.uroweb.org/guideline/neurourology/>.

1.4 Publication history

The EAU published the first Neuro-Urology Guidelines in 2003 with updates in 2008, 2014, and 2016. This 2017 document represents a limited update of the 2016 publication. The literature was assessed for all chapters.

1.5 Background

The function of the LUT is mainly storage and voiding of urine, which is regulated by the nervous system that co-ordinates the activity of the urinary bladder and bladder outlet. The part of the nervous system that regulates LUT function is disseminated from the peripheral nerves in the pelvis to highly specialised cortical areas. Any disturbance of the nervous system involved, can result in neuro-urological symptoms. The extent and location of the disturbance will determine the type of LUT dysfunction, which can be symptomatic or asymptomatic. Neuro-urological symptoms can cause a variety of long-term complications; the most significant being deterioration of renal function. Since symptoms and long-term complications do not correlate [5], it is important to identify patients with neuro-urological symptoms, and establish if they have a low or high risk of subsequent complications. The risk of developing upper urinary tract (UUT) damage and renal failure is much lower in patients with slowly progressive non-traumatic neurological disorders than in those with spinal cord injury or spina bifida [6]. In summary, treatment and intensity of follow-up examinations are based on the type of neuro-urological disorder and the underlying cause.

2. METHODS

2.1 Introduction

For the 2017 Neuro-Urology Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Neuro-Urology Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between January 1st 2013 and June 30th 2016. A total of 2,221 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <http://uroweb.org/guideline/neuro-urology/?type=appendices-publications>

Specific sections were updated by way of systematic reviews based on topics or questions prioritised by the Guideline Panel. These reviews were performed using standard Cochrane systematic review methodology; <http://www.cochranelibrary.com/about/about-cochrane-systematicreviews.html>.

Systematic review results included in the 2017 Neuro-Urology Guidelines are:

1. Continent catheterisable tubes/stomas in neuro-urological patients: A systematic review [7].
2. What is the long-term effectiveness and complication rate for bladder augmentation in patients with neurogenic bladder dysfunction [8]?

References used in this text are graded according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [9]. Additional information can be found in the general Methodology section of this print, and online at the EAU website; <http://www.uroweb.org/guideline/>. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

Publications ensuing from the systematic reviews have all been peer-reviewed. The 2015 Neuro-Urology Guidelines were subject to peer review prior to publication.

3. THE GUIDELINE

3.1 Epidemiology, aetiology and pathophysiology

3.1.1 Introduction

Neuro-urological symptoms may be caused by a variety of diseases and events affecting the nervous system controlling the LUT. The resulting neuro-urological symptoms depend predominantly on the location and the extent of the neurological lesion. There are no exact figures on the overall prevalence of neuro-urological disorders in the general population, but data are available on the prevalence of the underlying conditions and the relative risk of these for the development of neuro-urological symptoms. It is important to note that the majority of the data shows a very wide range of prevalence/incidence. This reflects the variability in the cohort (e.g. early or late stage disease) and the frequently small sample sizes, resulting in a low level of evidence in most published data (summarised in Table 1).

Table 1: Epidemiology of Neuro-Urological Disorders

<i>Suprapontine and pontine lesions and diseases</i>		
Neurological Disease	Frequency in General Population	Type and Frequency of Neuro-Urological Symptoms
Cerebrovascular accident (Strokes)	450 cases/100,000/yr (Europe) [10], 10% of cardiovascular mortality.	Nocturia - overactive bladder (OAB)-urgency urinary incontinence (UUI) - detrusor overactivity (DO), other patterns less frequent [11]. 57-83% of neuro-urological symptoms at 1 month post stroke, 71-80% spontaneous recovery at 6 months [12]. Persistence of urinary incontinence (UI) correlates with poor prognosis [13].
Dementias: Alzheimer's disease (80%) Vascular (10%) Other (10%)	6.4% of adults > 65 yrs [14].	OAB - UUI - DO 25% of incontinence in Alzheimer's disease, > 25% in other dementias: Lewy body, NPH, Binswanger, Nasu-Hakola, Pick Disease [15]. Incontinence 3 times more frequent in geriatric patients with dementia than without [16].

Parkinsonian syndrome (PS) Idiopathic Parkinson's disease (IPD): 75-80% of PS	2nd most prevalent neurodegenerative disease after Alzheimer's disease. Rising prevalence of IPD with age [17].	LUTS frequency 30% at onset, 70% after 5 yrs. Storage phase symptoms: Nocturia (78%) OAB - UUI - DO [18].
Non-IPD: Parkinson's-plus (18%): - Multiple system atrophy (MSA); - Progressive supranuclear palsy; - Corticobasal degeneration; - Dementia with Lewy bodies. Secondary Parkinson's (2%)	MSA is the most frequent non-IPD PS.	OAB and DO at the initial phase, intrinsic sphincter deficiency and impaired contractility appear as the disease progress. Complications of neuro-urological symptoms (infections) account for a major cause of mortality in MSA [19]. Impaired detrusor contractility seems to be the urodynamic finding distinguishing MSA from IPD [20, 21].
Brain tumours	26.8/100,000/yr in adults (> 19 yrs), (17.9 benign, 8.9 malignant) [22].	Incontinence occurs mainly in frontal location (part of frontal syndrome or isolated in frontal location) [23].
Cerebral palsy	Cerebral palsy: 3.1-3.6/1,000 in children aged 8 yrs [24].	62% of women and 58% of men with cerebral palsy suffer from UI [25] 70% detrusor overactivity. Recurrent urinary tract infection (UTI) and radiologic abnormalities in > 10% of cases [24, 25].
Traumatic brain injury	235/100,000/yr [26]	44% storage dysfunction. 38% voiding dysfunction, 60% urodynamic abnormalities [27].
Lesions and diseases between caudal brainstem and sacral spinal cord		
Spinal cord injury (SCI)	Prevalence of traumatic SCI in developed countries ranges from 280 to 906/million [28].	Neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD) (up to 95%) and detrusor underactivity (up to 83%) depending on the level of the lesion [29].
Spina bifida (SB)	Spina bifida 3-4/10,000 Lumbar and lumbosacral form are the most common (60%) [30].	Bladder function is impaired in up to 96% of SB patients [31].
Lesions and diseases of the peripheral nervous system		
Lumbar spine Degenerative disease Disk prolapse Lumbar canal stenosis	Male (5%) and female (3%) > 35 yr have had a lumbosacral episode related to disc prolapse. Incidence: approx. 5/100,000/yr More common in females > 45 yr.	26% difficulty to void and acontractile detrusor [32]. Detrusor underactivity (up to 83%) [29].
Iatrogenic pelvic nerve lesions	Rectal cancer. Cervical cancer (multimodal therapy, radiotherapy and surgery). Endometriosis surgery.	After abdomino-perineal resection (APR): 50% urinary retention. After total mesorectal excision (TME): 10-30% voiding dysfunction [33].
Peripheral neuropathy Diabetes Other causes of peripheral neuropathy causing neuro-urological symptoms: alcohol abuse; lumbosacral zona and genital herpes; Guillain Barré syndrome; porphyria; sarcoidosis	Worldwide, prevalence of pharmacologically treated diabetes 8.3% [34].	Urgency/frequency +/-incontinence [35]. Hyposensitive and detrusor underactivity at later phase [35].

Disseminated central diseases		
Multiple sclerosis (MS)	Prevalence: 83/100,000 in Europe [36].	10% of MS patients present with voiding dysfunction at disease onset, 75% of patients will develop it after 10 yrs of MS [37]. DO: 86% [37]. DSD: 35% [37]. Detrusor underactivity: 25% [37].

3.2 Classification systems

3.2.1 Introduction

Relevant definitions are found in the general ICS standardisation report [1, 2]. Section 3.2.2 lists the definitions from these references, partly adapted, and other definitions considered useful for clinical practice (Tables 2 and 3).

3.2.2 Definitions

Table 2: Definitions useful in clinical practice

Autonomic dysreflexia (AD)	Autonomic dysreflexia is a sudden and exaggerated autonomic response to various stimuli in patients with SCI or spinal dysfunction at or above level Th 6. It is defined as an increase in SBP > 20 mmHg from baseline [38]. Autonomic dysreflexia may be symptomatic (headache, blurred vision, stuffy nose, piloerection, flushing, sweating above the lesion level (vasodilatation), pale and cold skin (vasoconstriction) below the lesion level or asymptomatic (silent).
Bladder expression	Various manoeuvres aimed at increasing intravesical pressure in order to facilitate bladder emptying (abdominal straining, Valsalva's manoeuvre and Crede's manoeuvre) [3].
Bladder reflex triggering	Various manoeuvres performed by the patient or the therapist in order to elicit reflex detrusor contraction by exteroceptive stimuli (suprapubic tapping, thigh scratching and anal/rectal manipulation) [3].
Bladder sensation, absent	<i>During history taking</i> , the patient reports no sensation of bladder filling or desire to void [3]. <i>During filling cystometry</i> , the patient has no bladder sensation [3].
Bladder sensation, normal	<i>During history taking</i> , the patient is aware of bladder filling and increasing sensation up to a strong desire to void [3].
First sensation of bladder filling	The feeling, during filling cystometry, when the patient first becomes aware of the bladder filling [3]. <i>During filling cystometry</i> , can further be judged by the two following defined points and evaluated in relation to the bladder volume at that moment and in relation to the patient's symptomatic complaints [3].
First desire to void	The feeling, during filling cystometry, that would lead the patient to pass urine at the next convenient moment, but voiding can be delayed if necessary [3].
Strong desire to void	Persistent desire to void, during filling cystometry, without the fear of leakage [3].
Bladder sensation, increased	<i>During history taking</i> , the patient feels an early and persistent desire to void [3]. <i>During filling cystometry</i> , an early first sensation of bladder filling (or an early desire to void) and/or an early strong desire to void, which occurs at low bladder volume and which persists. It is a subjective assessment, not possible to quantify [3].

Bladder sensation, non-specific	<i>During history taking</i> , the patient reports no specific bladder sensation but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity [3]. <i>During filling cystometry</i> , may make the patient aware of bladder filling, for example, abdominal fullness or vegetative symptoms [3].
Bladder sensation, reduced	<i>During history taking</i> , the patient is aware of bladder filling but does not feel a definite desire to void [3]. <i>During filling cystometry</i> , a diminished sensation throughout bladder filling [3].
Catheterisation	Technique for bladder emptying employing a catheter to drain the bladder or a urinary reservoir [3].
Catheterisation, indwelling	An indwelling catheter remains in the bladder, urinary reservoir or urinary conduit for a period of time longer than one emptying [3].
Catheterisation, intermittent (IC)	Drainage or aspiration of the bladder or a urinary reservoir with subsequent removal of the catheter [3]. When not specified “self”, it is performed by an attendant (e.g. doctor, nurse or relative).
Aseptic IC	Use of a sterile technique. This implies genital disinfection and the use of sterile catheters and instruments/gloves [3].
Clean IC	Use of a clean technique. This implies ordinary washing techniques and use of disposable or cleansed reusable catheters [3].
Intermittent self-catheterisation	Performed by the patient him/herself [3].
Daytime frequency, increased	Complaint by the patient who considers that he/she voids too often by day. This term is equivalent to pollakiuria used in many countries [3]. Many population-based studies of OAB have defined frequency as either eight or more voids/day, or eight or more voids/24 hours [39].
Diary, bladder	Records the times of micturitions and voided volumes, incontinence episodes, pad usage and other information such as fluid intake, the degree of urgency and the degree of incontinence [3].
Frequency volume chart (FVC)	Records the volumes voided as well as the time of each micturition, day and night, for at least 24 hours [3].
Micturition time chart	Records only the times of micturitions, day and night, for at least 24 hours [3].
Enuresis	Any involuntary loss of urine. If it is used to denote incontinence during sleep, it should always be qualified with the adjective “nocturnal” [3].
Hesitancy	Difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine [3].
Intermittent stream (Intermittency)	Urine flow which stops and starts, on one or more occasions, during micturition [3].
Motor neuron lesion, lower (LMNL)	Lesion resulting from damage to motor neurons of the ventral horns or motor neuron of the cranial nerve nuclei, or resulting from interruption of the final common pathway connecting the neuron via its axon with the muscle fibres it innervates (the motor unit) [3].
Motor neuron lesion, upper (UMNL)	Lesion resulting from damage to cortical neurons that give rise to corticospinal and corticobulbar tracts. It may occur at all levels of the neuraxis from the cerebral cortex to the spinal cord. When rostral to the pyramidal decussation of the caudal medulla, they result in deficits below the lesion, on the contralateral side. When caudal to the pyramidal decussation, they result in deficits below the lesion, on the ipsilateral side [40].
Neurogenic shock	Loss of vascular tone in part of the body deprived of supraspinal control. It commonly occurs during the acute period following spinal cord injury (SCI) and is associated with failure of the sympathetic nervous system. In this condition, systolic blood pressure < 90 mmHg in the supine posture is not the result of low intravascular volume (e.g. blood loss, dehydration, sepsis, cardiac disorders) [38].
Spinal shock	Characterised by marked reductions in spinal reflex activity below the level of injury [38].
Nocturia	The complaint that the individual has to wake at night one or more times to void [3]. Each void is preceded and followed by sleep.

Nocturnal polyuria	It is present when an increased proportion of the 24-hour output occurs at night (normally during the 8 hours whilst the patient is in bed). The night time urine output excludes the last void before sleep but includes the first void of the morning [3].
Neurogenic lower urinary tract dysfunction (NLUTD)	Lower urinary tract dysfunction (LUTD) secondary to confirmed pathology of the nervous supply.
Orthostatic hypotension	Symptomatic (dizziness, headache or neck ache, fatigue) or asymptomatic decrease in blood pressure defined as a drop of at least 20 mmHg systolic or 10 mmHg diastolic within 3 minutes of moving from the supine to an upright position [2, 39].
Overactive bladder syndrome (also urge syndrome or urgency-frequency syndrome)	Urgency, with or without urge incontinence, usually with frequency and nocturia [3].
Pain, genital and lower urinary tract	Abnormal sensations felt by the individual as pain, discomfort and pressure. Should be characterised by type, frequency, duration, precipitating and relieving factors and by location [3].
Bladder pain	<i>During history taking</i> , pain that is felt suprapubically or retropubically, and usually increases with bladder filling, it may persist after voiding [3]. <i>During filling cystometry</i> , is an abnormal finding [3].
Pelvic pain	Is less well defined than, for example, bladder, urethral or perineal pain and is less clearly related to the micturition cycle or to bowel function and is not localised to any single pelvic organ [3].
Perineal pain	In females, between the posterior fourchette (posterior lip of the introitus) and the anus. In males, between the scrotum and the anus [3].
Scrotal pain	May or may not be localised, for example to the testis, epididymis, cord structures or scrotal skin [3].
Urethral pain	Pain that is felt in the urethra and the individual indicates the urethra as the site [3].
Vaginal pain	Is felt internally, above the introitus [3].
Vulvar pain	Is felt in and around the external genitalia [3].
Pelvic organ prolapse	Descent of one or more of the anterior vaginal wall, the posterior vaginal wall, and the apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy. Absence of prolapse is defined as stage 0 support; prolapse can be staged from stage I to stage IV [3].
Slow stream	Perception of reduced urine flow, usually compared to previous performance or in comparison to others [3].
Spinal cord injury	Incomplete: if partial preservation of sensory and/or motor functions is found below the neurological level and includes the lowest sacral segment. Complete: when there is an absence of sensory and motor function in the lowest sacral segment [41].
Cauda equina	Injuries affecting the cauda equina and generally causing an acontractile or lower motor neuron picture affecting the LUT, distal bowel and sexual function [38].
Conal	Injuries affecting the conus medullaris of the spinal cord and often causing a mixed lesion to the LUT, distal bowel and sexual functions with a resultant either overactive or acontractile picture [38].
Supraconal	Injuries occurring above the conus medullaris. In general, supraconal injuries cause an overactive or upper motor neuron pattern of damage affecting the LUT, distal bowel and sexual functions [38].
Straining to void	Muscular effort used to either initiate, maintain or improve the urinary stream [3].
Terminal dribble	Prolonged final part of micturition, when the flow has slowed to a trickle/dribble [3].
Urgency	The complaint of a sudden compelling desire to pass urine which is difficult to defer [3].
Urinary incontinence (UI)	Complaint of any involuntary leakage of urine [3].

Stress urinary incontinence (SUI)	Complaint of involuntary leakage on effort or exertion, or on sneezing or coughing [3].
Urge urinary incontinence (UII)	Complaint of involuntary leakage accompanied by or immediately preceded by urgency [3].
Mixed urinary incontinence	Complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing [3].
Continuous urinary incontinence	Complaint of continuous leakage [3].
Voided volume, maximum	The largest volume of urine voided during a single micturition which is determined either from the frequency/volume chart or bladder diary [3].

Table 3: Definitions useful when interpreting urodynamic studies.

Bladder compliance	Relationship between change in bladder volume and change in detrusor pressure. Compliance is calculated by dividing the volume change (ΔV) by the associated change in detrusor pressure (Δp_{det}) during the change in bladder volume ($C = \Delta V / \Delta p_{det}$). It is expressed in mL/cm H ₂ O [3].
Bladder filling, artificial	Filling the bladder, via a catheter, with a specified liquid at a specified rate [3].
Bladder filling, natural	The bladder is filled by the production of urine rather than by an artificial medium [3].
Bladder outlet obstruction	Generic term for obstruction during voiding, characterised by increased detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow rate and detrusor pressure [40].
Cystometric capacity	The bladder volume at the end of the filling cystometrogram, when "permission to void" is usually given. The volume voided together with any residual urine [3].
Maximum anaesthetic bladder capacity	The volume to which the bladder can be filled under deep general or spinal anaesthetic and should be qualified according to the type of anaesthesia used, the speed, the length of time, and the pressure at which the bladder is filled [3].
Maximum cystometric capacity	In patients with normal sensation, the volume at which the patient feels they can no longer delay micturition (has a strong desire to void) [3].
Detrusor function, normal	Allows bladder filling with little or no change in pressure. No involuntary phasic contractions occur despite provocation [40]. Normal voiding is achieved by a voluntarily initiated continuous detrusor contraction that leads to complete bladder emptying within a normal time span, and in the absence of obstruction. For a given detrusor contraction, the magnitude of the recorded pressure rise will depend on the degree of outlet resistance [3].
Detrusor overactivity	Urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [3].
Detrusor overactivity incontinence	Incontinence due to an involuntary detrusor contraction [3].
Idiopathic detrusor overactivity	When there is no defined cause [3].
Phasic detrusor overactivity	Is defined by a characteristic wave form and may or may not lead to UI [3].
Neurogenic detrusor overactivity	When there is a relevant neurological condition present [3].
Terminal detrusor overactivity	A single, involuntary detrusor contraction, occurring at cystometric capacity, which cannot be suppressed and results in incontinence usually resulting in bladder emptying (voiding) [3].
Detrusor sphincter dyssynergia (DSD)	A detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle. Occasionally, flow may be prevented altogether [3]. This term is specific to patients with a neurological diagnosis.

Detrusor underactivity	Contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span [3].
Acontractile detrusor	Detrusor that cannot be demonstrated to contract during urodynamic studies [3].
Dysfunctional voiding	Intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the peri-urethral striated muscle during voiding in neurologically normal individuals [3].
Filling cystometry	Method by which the pressure/volume relationship of the bladder is measured during bladder filling [3].
Filling rate, physiological	Filling rate less than the predicted maximum - body weight (kg) /4 in mL/min [3, 42].
Filling rate, non-physiological	Filling rate greater than the predicted maximum filling rate [3, 42].
Leak point pressure, abdominal (ALPP)	The intravesical pressure at which urine leakage occurs due to increased abdominal pressure in the absence of a detrusor contraction [3].
Leak point pressure, detrusor (DLPP)	The lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure [3].
Non-relaxing urethral sphincter obstruction	Characterised by a non-relaxing, obstructing urethra resulting in reduced urine flow. Usually occurs in individuals with a neurological lesion [3].
Post void residual (PVR)	The volume of urine left in the bladder at the end of micturition [3].
Pressure flow study	Method by which the relationship between pressure in the bladder and urine flow rate is measured during bladder emptying [3].
Provocative manoeuvres	Techniques used during urodynamics in an effort to provoke detrusor overactivity, for example, rapid filling, use of cooled or acid medium, postural changes and hand washing [3].
Urethral closure mechanism, incompetent	Allows leakage of urine in the absence of a detrusor contraction [3].
Urethral relaxation incontinence	Leakage due to urethral relaxation in the absence of raised abdominal pressure or detrusor overactivity [3].
Urethral closure mechanism, normal	Maintains a positive urethral closure pressure during bladder filling even in the presence of increased abdominal pressure, although it may be overcome by detrusor overactivity.
Urethral pressure	The fluid pressure needed to just open a closed urethra [3].
Urethral pressure, maximum	The maximum pressure of the measured profile [3].
Urethral pressure profile	A graph indicating the intraluminal pressure along the length of the urethra [3].
Urethral closure pressure profile	Is given by the subtraction of intravesical pressure from urethral pressure [3].
Urethral closure pressure, maximum (MUCP)	The maximum difference between the urethral pressure and the intravesical pressure [3].
Urethral functional profile length	The length of the urethra along which the urethral pressure exceeds intravesical pressure in women [3].
Urethral pressure “transmission” ratio	The increment in urethral pressure on stress as a percentage of the simultaneously recorded increment in intravesical pressure [3].
Urodynamic stress incontinence	The involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction [3].
Urodynamic study, ambulatory	Functional test of the lower urinary tract, utilising natural filling, and reproducing the subject’s every day activities [3].
Urodynamic study, conventional	Normally takes place in the urodynamic laboratory and usually involve artificial bladder filling [3].

3.3 Diagnostic evaluation

3.3.1 Introduction

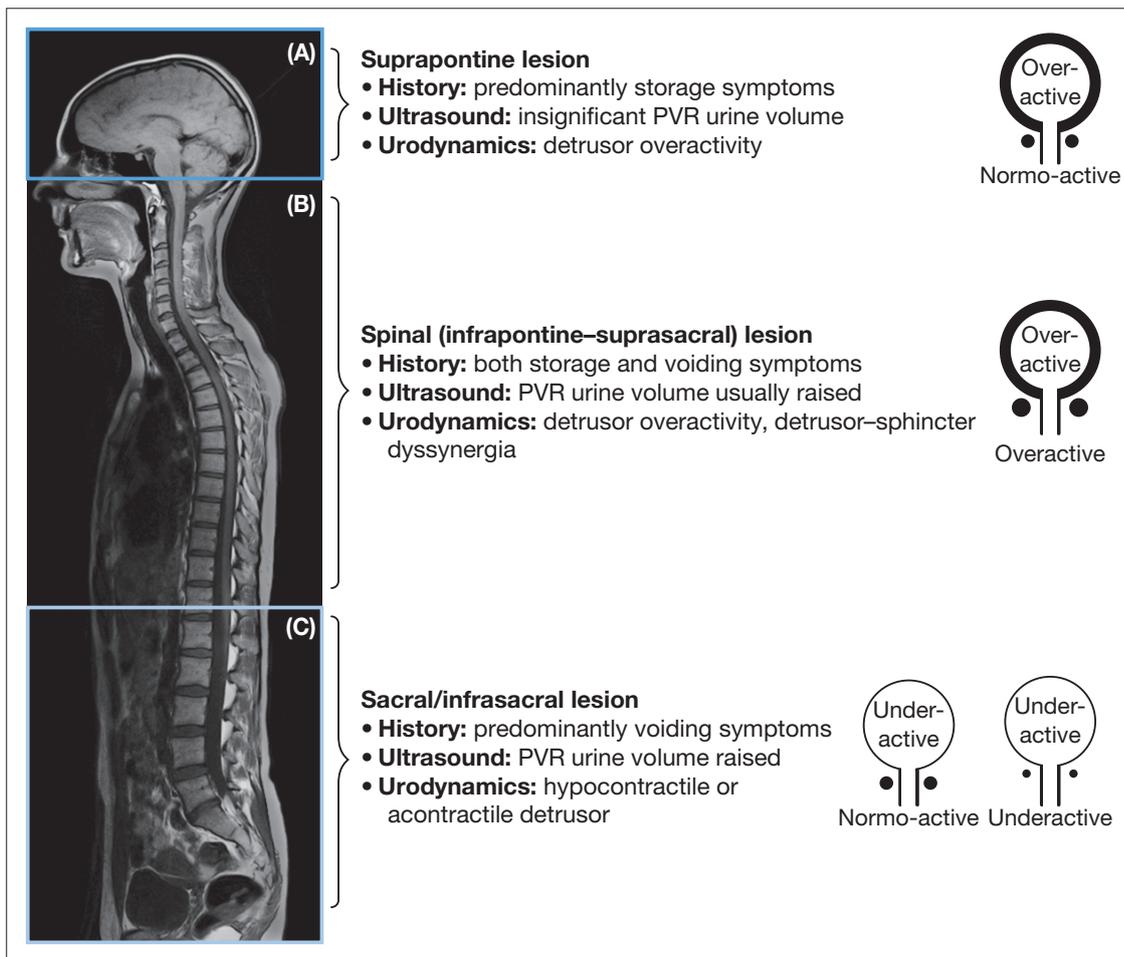
The normal physiological function of the LUT depends on an intricate interplay between the sensory and motor nervous systems. When diagnosing neuro-urological symptoms, the aim is to describe the type of dysfunction

involved. A thorough medical history, physical examination and bladder diary are mandatory before any additional diagnostic investigations can be planned. Results of the initial evaluation are used to decide the patient's long-term treatment and follow-up.

3.3.2 Classification systems

The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. A very simple classification system for use in daily clinical practice to decide on the appropriate therapeutic approach is provided in Figure 1 [6].

Figure 1: Patterns of lower urinary tract dysfunction following neurological disease



The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. Panel (A) denotes the region above the pons, panel (B) the region between the pons and the sacral cord and panel (C) the sacral cord and infrasacral region. Figures on the right show the expected dysfunctional states of the detrusor-sphincter system. Figure adapted from Panicker et al. [6] with permission from Elsevier. PVR = post-void residual.

3.3.3 Timing of diagnosis and treatment

Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders [43]. This helps to prevent irreversible changes within the LUT, even in the presence of normal reflexes [44, 45]. Furthermore, urological symptoms can be the presenting feature of neurological pathology [46, 47]. Early intervention can prevent irreversible deterioration of the LUT and UUT [48].

3.3.4 Patient history

History taking should include past and present symptoms and disorders (Table 4). It is the cornerstone of evaluation, as the answers will aid in diagnostic investigations and treatment options.

- In non-traumatic neuro-urological patients with an insidious onset, a detailed history may find that the condition started in childhood or adolescence [49].

- Urinary history consists of symptoms associated with both urine storage and emptying.
- Bowel history is important because patients with neuro-urological symptoms may also have related neurogenic bowel dysfunction [50].
- Sexual function may be impaired because of the neuro-urological condition [51].
- Special attention should be paid to possible warning signs and symptoms (e.g. pain, infection, haematuria and fever) requiring further investigation.
- Patients with SCI usually find it difficult to report UTI-related symptoms accurately [52, 53].
- The presence of urinary, bowel and sexual symptoms without neurological symptoms could be suggestive of an underlying neurological disease or condition.
- Ambulatory status after acute SCI does not predict presence or absence of unfavourable urodynamic parameters [54].

Table 4: History taking in patients with suspected neuro-urological disorder

Past history
Childhood through to adolescence and into adulthood
Hereditary or familial risk factors
Specific female: Menarche (age); this may suggest a metabolic disorder
Obstetric history
History of diabetes
Diseases, e.g. multiple sclerosis, parkinsonism, encephalitis, syphilis
Accidents and operations, especially those involving the spine and central nervous system
Present history
Present medication
Lifestyle (smoking, alcohol and drugs); may influence urinary, sexual and bowel function
Quality of life
Specific urinary history
Onset of urological history
Relief after voiding; to detect the extent of a neurological lesion in the absence of obstructive uropathy
Bladder sensation
Initiation of micturition (normal, precipitate, reflex, strain, Credé)
Interruption of micturition (normal, paradoxical, passive)
Enuresis
Mode and type of voiding (catheterisation)
Frequency, voided volume, incontinence, urgency episodes
Sexual history
Genital or sexual dysfunction symptoms
Sensation in genital area
Specific male: erection, (lack of) orgasm, ejaculation
Specific female: dyspareunia, (lack of) orgasm
Bowel history
Frequency and faecal incontinence
Desire to defecate
Defecation pattern
Rectal sensation
Initiation of defecation (digitation)
Neurological history
Acquired or congenital neurological condition
Mental status and comprehension
Neurological symptoms (somatic and sensory), with onset, evolution and any treatment
Spasticity or autonomic dysreflexia (especially in lesions at or above level Th 6)
Mobility and hand function

3.3.4.1 Bladder diaries

Bladder diaries provide data on the number of voids, voided volume, pad weight and incontinence and urgency episodes. Although a 24 hour bladder diary (recording should be done for three consecutive days) is reliable in women with UI [55, 56], no research has been done on bladder diaries in neuro-urological patients.

Nevertheless, bladder diaries are considered a valuable diagnostic tool.

3.3.5 Patient quality of life questionnaires

An assessment of the patient's present and expected future quality of life (QoL) is important to evaluate the effect of any therapy. Quality of life is an essential aspect of the overall management of neuro-urological patients, for example when evaluating treatment related changes on a patient's QoL [57]. The type of bladder management has been shown to affect health-related QoL (HRQoL) in patients with SCI [58] and MS [59]. Other research has also highlighted the importance of urological treatment and its impact on the urodynamic functionality of the neuro-urological patient in determining patient QoL [60].

In recent years a proliferation in the number of questionnaires to evaluate symptoms and QoL has been seen. Condition-specific questionnaires can be used to assess symptom severity and the impact of symptoms on QoL. A patient's overall QoL can be assessed using generic questionnaires. It is important that the questionnaire of choice has been validated in the neuro-urological population, and that it is available in the language that it is to be used in.

3.3.5.1 Questions

- Which validated patient questionnaires are available for neuro-urological patients?
- Which questionnaires are the most appropriate for use in neuro-urological patients?

3.3.5.2 Evidence

Three condition-specific questionnaires for urinary or bowel dysfunction and QoL have been developed specifically for adult neuro-urological patients [61]. In MS and SCI patients the Qualiveen [62, 63] is validated and can be used for urinary symptoms. A short form of the Qualiveen is available [62, 63] and it has been translated into various languages [64-67]. The Neurogenic Bladder Symptom Score (NBSS) has been validated in neurological patients to measure urinary symptoms and their consequences [68]. The QoL scoring tool related to Bowel Management (QoL-BM) [69] can be used to assess bowel dysfunction in MS and SCI patients.

In addition, sixteen validated questionnaires that evaluate QoL and assess urinary symptoms as a subscale or question in neuro-urological patients have been identified [70] (Table 5). The condition-specific Incontinence-Quality of Life (I-QoL) questionnaire which was initially developed for the non-neurological population has now also been validated for neuro-urological patients [71].

A patient's overall QoL can be assessed by generic HRQoL questionnaires, the most commonly used being the Incontinence Quality of Life Instrument (I-QOL), King's Health Questionnaire (KHQ), or the Short Form 36-item and 12-item Health Survey Questionnaires (SF-36, SF-12) [61]. In addition, the quality-adjusted life year (QALY), quantifies outcomes, by weighing years of life spent in a specified health state, adjusted by a factor representing the value placed by society or patients on their specific health state [72].

No evidence was found for which validated questionnaires are the most appropriate for use, since no quality criteria for validated questionnaires have been assessed [73].

Table 5: Patient questionnaires

Questionnaire	Underlying neurological disorder	Bladder	Bowel	Sexual function
FAMS [74]	MS	X		X
FILMS [75]	MS	X	X	
HAQUAMS [76]	MS	X	X	X
IQOL [71]	MS, SCI	X		X
MDS [77]	MS	X	X	
MSISQ-15 / MSISQ-19 [78, 79]	MS	X	X	X
MSQLI [80]	MS	X	X	X
MSQoL-54 [81]	MS	X	X	X
MSWDQ [82]	MS	X	X	
NBSS [83]	MS, SCI, Congenital neurogenic bladder	X		
QoL-BM [69]	SCI		X	
Qualiveen/SF-Qualiveen [63, 84]	MS, SCI	X		X
RAYS [85]	MS	X		X
RHSCIR [86]	SCI	X	X	X
Fransceschini [85]	SCI	X	X	X

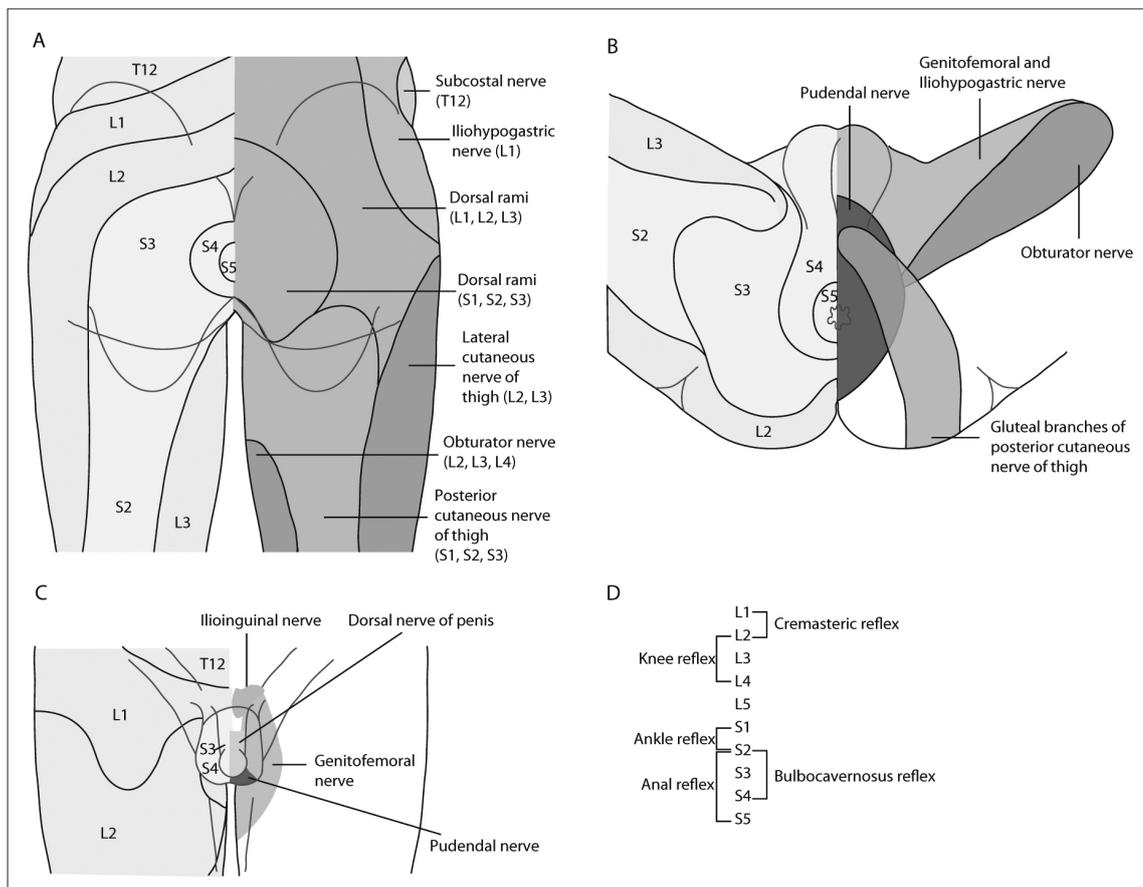
3.3.6 Physical examination

In addition to a detailed patient history, attention should be paid to possible physical and intellectual disabilities with respect to the planned investigations. Neuro-urological status should be described as completely as possible (Figure 2). Patients with a high spinal cord lesion or supraspinal neurological lesions may suffer from a significant drop in blood pressure when moved into a sitting or standing position. All sensations and reflexes in the urogenital area must be tested. Furthermore, detailed testing of the anal sphincter and pelvic floor functions must be performed (Figure 2). It is essential to have this clinical information to reliably interpret later diagnostic investigations.

3.3.6.1 Autonomic dysreflexia

Autonomic dysreflexia is a sudden and exaggerated autonomic response to various stimuli in patients with SCI or spinal dysfunction. It generally manifests at or above level Th 6. The stimulus can be distended bladder or bowel. For example, iatrogenic stimuli during cystoscopy or urodynamics can trigger AD [87]. It can also be secondary to sexual stimulation or a noxious stimulus, e.g. infected toe nail or pressure sore. Autonomic dysreflexia is defined by an increase in systolic blood pressure > 20 mmHg from baseline [38] and can have life-threatening consequences if not properly managed [88].

Figure 2: Lumbosacral dermatomes, cutaneous nerves, and reflexes



The physical examination includes testing sensations and reflexes mediated through the lower spinal cord. Abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of the lesion. Distribution of dermatomes (areas of skin mainly supplied by a single spinal nerve) and cutaneous nerves over the perianal region and back of the upper thigh (A), the perineum [89] (B), male external genitalia [90] (C) and root values of lower spinal cord reflexes (D). Figure adapted from Panicker et al. [6] with parts A-C adapted from Standring [91], both with permission from Elsevier.

Table 6: Neurological items to be specified

Sensation S2-S5 (both sides)
Presence (increased/normal/reduced/absent)
Type (light touch/pin prick)
Affected dermatomes
Reflexes (increased/normal/reduced/absent)
Bulbocavernous reflex
Perianal/anal reflex
Knee and ankle reflexes
Plantar responses (Babinski)
Anal sphincter tone
Presence (increased/normal/reduced/absent)
Voluntary contractions of anal sphincter and pelvic muscles (increased/normal/reduced/absent)
Prostate palpation
Descensus (prolapse) of pelvic organs

3.3.6.2 Recommendations for history taking and physical examination

History taking	LE	GR*
Take an extensive general history, concentrating on past and present symptoms including urinary, sexual, bowel, and neurological functions.	4	A
Pay special attention to the possible existence of alarm signs (e.g. pain, infection, haematuria, fever) that warrant further specific diagnosis.	4	A
Take a specific history for each of the four mentioned functions.	4	A
Assess quality of life when evaluating and treating the neuro-urological patient.	2a	B
Use available validated tools including the Qualiveen and I-QoL for urinary symptoms and the QoL-BM for bowel dysfunction in multiple sclerosis and spinal cord injury patients. In addition, generic (SF-36 or KHQ) questionnaires can be used.	1a	A
Physical examination		
Acknowledge individual patient disabilities when planning further investigations.	4	A
Describe the neurological status as completely as possible, sensations and reflexes in the urogenital area must all be tested.	4	A
Test the anal sphincter and pelvic floor functions.	4	A
Perform urinalysis, blood chemistry, bladder diary, residual and free flowmetry, incontinence quantification and urinary tract imaging.	4	A

* All grade A recommendations are based on panel consensus.

I-QoL = Incontinence Quality of Life Instrument; QoL-BM = Quality of Life Bowel Management scoring tool;
KHQ = King's Health Questionnaire; SF-36 = Short Form 36-item Health Survey Questionnaires.

3.3.7 Urodynamics

3.3.7.1 Introduction

Urodynamic investigation is the only method that can objectively assess the function and dysfunction of the LUT. In neuro-urological patients, invasive urodynamic investigation is even more challenging than in general patients. Any technical source of artefacts must be critically considered. It is essential to maintain the quality of the urodynamic recording and its interpretation [1]. Same session repeat urodynamic investigations are crucial in clinical decision making, since repeat measurements may yield completely different results [92].

In patients at risk for AD, it is advisable to measure blood pressure during the urodynamic study [93]. The rectal ampulla should be empty of stool before the start of the investigation. All urodynamic findings must be reported in detail and performed, according to the ICS technical recommendations and standards [1, 94].

3.3.7.2 Urodynamic tests

Free uroflowmetry and assessment of residual urine: Provides a first impression of the voiding function and is compulsory prior to planning any invasive urodynamics in patients able to void. For reliable information, it should be repeated at least two to three times [1]. Possible pathological findings include a low flow rate, low voided volume, intermittent flow, hesitancy and residual urine. Care must be taken when assessing the results in patients unable to void in a normal position, as both flow pattern and rate may be modified by inappropriate positions.

Filling cystometry: This test is the only method for quantifying the patient's filling function. The status of LUT function must be documented during the filling phase. However, this technique has limited use as a solitary procedure. It is much more effective combined with bladder pressure measurement during micturition and is even more effective in video-urodynamics.

The bladder should be empty at the start of filling. A physiological filling rate should be used with body-warm saline. Possible pathological findings include DO, low bladder compliance, abnormal bladder sensations, incontinence, and an incompetent or relaxing urethra.

Detrusor leak point pressure (DLPP) [95]: Appears to have no use as a diagnostic tool. Some positive findings have been reported [96, 97], but sensitivity is too low to estimate the risk to the UUT or for secondary bladder damage [98, 99].

Pressure flow study: Reflects the co-ordination between detrusor and urethra or pelvic floor during the voiding phase. It is even more powerful if combined with filling cystometry and video-urodynamics. Lower urinary tract function must be recorded during the voiding phase. Possible pathological findings include detrusor underactivity, bladder outlet obstruction (BOO), DSD, a high urethral resistance, and residual urine.

Most types of obstruction caused by neuro-urological disorders are due to DSD [100, 101], non-relaxing urethra, or non-relaxing bladder neck [102, 103]. Pressure-flow analysis mainly assesses the amount of mechanical obstruction caused by the urethra's inherent mechanical and anatomical properties and has limited value in patients with neuro-urological disorders.

Electromyography (EMG): Reflects the activity of the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter and the striated pelvic floor muscles. Correct interpretation may be difficult due to artefacts introduced by other equipment. In the urodynamic setting, an EMG is useful as a gross indication of the patient's ability to control the pelvic floor. Possible pathological findings include inadequate recruitment upon specific stimuli (e.g. bladder filling, involuntary detrusor contractions, onset of voiding, coughing, Valsalva manoeuvre) suggesting a diagnosis of DSD [104].

Urethral pressure measurement: Has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings [105].

Video-urodynamics: Is the combination of filling cystometry and pressure flow studies with imaging. It is the optimum procedure for urodynamic investigation in neuro-urological disorders. Possible pathological findings include all those described in the cystometry and the pressure flow study sections, and any morphological pathology of the LUT and reflux to the UUT [106].

Ambulatory urodynamics: This is the functional investigation of the urinary tract, which predominantly uses the natural filling of the urinary tract to reproduce the patient's normal activity. Although this type of study might be considered when conventional urodynamics does not reproduce the patient's symptoms, its role in the neuro-urological patient still needs to be determined [107, 108].

Triggered tests during urodynamics: Lower urinary tract function can be provoked by coughing, triggered voiding, or anal stretch. Fast-filling cystometry with cooled saline (the 'ice water test') will discriminate between upper and lower motor neuron lesions [109, 110]. Patients with UMNL develop a detrusor contraction if the detrusor is intact, while patients with LMNL do not. However, the test does not seem to be fully discriminative in other types of patients [111].

Previously, a positive bethanechol test [112] (detrusor contraction > 25 cm H₂O) was thought to indicate detrusor denervation hypersensitivity and the muscular integrity of an acontractile detrusor. However, in practice, the test has given equivocal results. A variation of this method was reported using intravesical electromotive administration of the bethanechol [113], but there was no published follow-up. Currently, there is no indication for this test.

3.3.7.3 Specialist uro-neurophysiological tests

The following tests are advised as part of the neurological work-up [114]:

- electromyography (in a neurophysiological setting) of pelvic floor muscles, urethral sphincter and/or anal sphincter;
- nerve conduction studies of pudendal nerve;
- reflex latency measurements of bulbocavernosus and anal reflex arcs;
- evoked responses from clitoris or glans penis;
- sensory testing on bladder and urethra.

Other elective tests, for specific conditions, may become obvious during the work-up and urodynamic investigations.

3.3.7.4 Recommendations for urodynamics and uro-neurophysiology

Recommendations	LE	GR
Record a bladder diary.	3	A
Non-invasive testing is mandatory before invasive urodynamics is planned.	4	A*
Perform a urodynamic investigation to detect and specify lower urinary tract (dys-)function, use same session repeat measurement as it is crucial in clinical decision making.	1b	A
Use video-urodynamics for invasive urodynamics in neuro-urological patients. If this is not available, then perform a filling cystometry continuing into a pressure flow study.	4	A*
Use a physiological filling rate and body-warm saline.	4	A*
Specific uro-neurophysiological tests are elective procedures and should only be carried out in specialised settings.	4	C

*Upgraded based on panel consensus.

3.3.8 Renal function

In many patients with neuro-urological disorders, the UUT is at risk, particularly in patients who develop high detrusor pressure during the filling phase. Although effective treatment can reduce this risk, there is still a relatively high incidence of renal morbidity [115]. Patients with SCI or SB have a substantially higher risk of developing renal failure compared with patients with slowly progressive non-traumatic neurological disorders, such as MS and Parkinson's disease (PD) [116].

Caregivers must be informed of this risk and instructed to watch carefully for any signs or symptoms of a possible deterioration in the patient's renal function. There are no high level evidence publications available which show the optimal management to preserve renal function in these patients [117].

3.4 Disease management

3.4.1 Introduction

The primary aims for treatment of neuro-urological symptoms, and their priorities, are [118, 119]:

- protection of the UUT;
- achievement (or maintenance) of urinary continence;
- restoration of the LUT function;
- improvement of the patient's QoL.

Further considerations are the patient's disability, cost-effectiveness, technical complexity and possible complications [119].

Renal failure is the main mortality factor in SCI patients who survive the trauma [120, 121]. Keeping the detrusor pressure during both the filling and voiding phases within safe limits significantly reduces the mortality from urological causes in these patients [122-124] and has consequently become the top priority in the treatment of patients with neuro-urological symptoms [118, 119].

In patients with high detrusor pressure during the filling phase (DO, low bladder compliance), treatment is aimed primarily at conversion of an overactive, high-pressure bladder into a low-pressure reservoir despite the resulting residual urine [118]. Reduction of the detrusor pressure contributes to urinary continence, and consequently to social rehabilitation and QoL. It is also pivotal in preventing UTIs [125, 126]. Complete continence, however, cannot always be obtained.

3.4.2 Non-invasive conservative treatment

3.4.2.1 Assisted bladder emptying - Credé manoeuvre, Valsalva manoeuvre, triggered reflex voiding

Incomplete bladder emptying is a serious risk factor for UTI, high intravesical pressure during the filling phase, and incontinence. Methods to improve the voiding process are therefore practiced.

Bladder expression (Credé manoeuvre) and voiding by abdominal straining (Valsalva manoeuvre): The downwards movement of the lower abdomen by suprapubic compression (Credé) or by abdominal straining (Valsalva) leads to an increase in intravesical pressure, and generally also causes a reflex sphincter contraction [127, 128]. The latter may increase bladder outlet resistance and lead to inefficient emptying. The high pressures created during these procedures are hazardous for the urinary tract [129, 130]. Therefore, their use should be discouraged unless urodynamics show that the intravesical pressure remains within safe limits [119].

Long-term complications are unavoidable for both methods of bladder emptying [128]. The already weak pelvic floor function may be further impaired, thus introducing or exacerbating already existing stress urinary incontinence (SUI) [130].

Triggered reflex voiding: Stimulation of the sacral or lumbar dermatomes in patients with UMNL can elicit a reflex detrusor contraction [130]. The risk of high pressure voiding is present and interventions to decrease outlet resistance may be necessary [131]. Triggering can induce AD, especially in patients with high level SCI (at or above Th 6) [132]. All assisted bladder emptying techniques require low outlet resistance. Even then, high detrusor pressures may still be present. Hence, patients need dedicated education and close urodynamic and urological surveillance [130, 133-135].

Note: In the literature, including some of the references cited here, the concept “reflex voiding” is sometimes used to cover all three assisted voiding techniques described in this section.

External appliances: Social continence may be achieved by collecting urine during incontinence, for instance using pads [119]. Condom catheters with urine collection devices are a practical method for men [119]. The infection risk must be closely observed [119]. The penile clamp is absolutely contraindicated in case of DO or low bladder compliance because of the risk of developing high intravesical pressure and pressure sores/necrosis in cases of altered/absent sensations.

3.4.2.2 Neuro-urological rehabilitation

3.4.2.2.1 Bladder rehabilitation including electrical stimulation

The term bladder rehabilitation summarises treatment options that aim to re-establish bladder function in patients with neuro-urological symptoms. Strong contraction of the urethral sphincter and/or pelvic floor, as well as anal dilatation, manipulation of the genital region, and physical activity inhibit micturition in a reflex manner [119, 136]. The first mechanism is affected by activation of efferent nerve fibres, and the latter ones are produced by activation of afferent fibres [98]. Electrical stimulation of the pudendal nerve afferents strongly inhibits the micturition reflex and detrusor contraction [137]. This stimulation might then support the restoration of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level [119, 138]. Evidence for bladder rehabilitation using electrical stimulation in neurological patients is mainly based on small non-comparative studies with high risk of bias.

Peripheral temporary electrostimulation: Tibial nerve stimulation and transcutaneous electrical nerve stimulation might be effective and safe for treating neurogenic lower urinary tract dysfunction, but more reliable evidence from well-designed RCTs is required to reach definitive conclusions [138, 139].

Peripheral temporary electrostimulation combined with pelvic floor muscle training and biofeedback: In MS patients, combining active neuromuscular electrical stimulation with pelvic floor muscle training and EMG biofeedback can achieve a substantial reduction of neuro-urological symptoms [140]. This treatment combination seems to be more effective than either therapy alone [141, 142].

Intravesical electrostimulation: Intravesical electrostimulation can increase bladder capacity and improve bladder compliance and bladder filling sensation in patients with incomplete SCI or myelomeningocele (MMC) [143]. In patients with neurogenic detrusor underactivity, intravesical electrostimulation may also improve voiding and reduce residual volume [144, 145].

Repetitive transcranial magnetic stimulation: Although improvement of neuro-urological symptoms has been described in PD and MS patients, this technique is still under investigation [146, 147].

Summary: To date, bladder rehabilitation techniques are mainly based on electrical or magnetic stimulation. However, there is a lack of well-designed studies.

3.4.2.3 Drug treatment

A single, optimal, medical therapy for neuro-urological symptoms is not yet available. Commonly, a combination of different therapies (e.g. intermittent catheterisation and antimuscarinic drugs) is advised to prevent urinary tract damage and improve long-term outcomes, particularly in patients with a suprasacral SCI or MS [130, 148-150].

3.4.2.3.1 Drugs for storage symptoms

Antimuscarinic drugs: They are the first-line choice for treating NDO, increasing bladder capacity and

reducing episodes of UI secondary to NDO by the inhibition of parasympathetic pathways [119, 151-157]. Antimuscarinic drugs have been used for many years to treat patients with NDO [154, 155, 158], and the responses of individual patients to antimuscarinic treatment are variable. Despite a meta-analysis confirming the clinical and urodynamic efficacy of antimuscarinic therapy compared to placebo in adult NDO, a more recent integrative review has indicated that the information provided is still too limited for clinicians to be able to match trial data to the needs of individual patients with SCI mainly because of the lack of standardised clinical evaluation tools such as the ASIA, bladder diary and validated symptoms score. [155, 159].

Higher doses or a combination of antimuscarinic agents may be an option to maximise outcomes in neurological patients [156, 157, 160-163]. However, these drugs have a high incidence of adverse events, which may lead to early discontinuation of therapy [155, 156].

Choice of antimuscarinic agent: Oxybutynin [119, 154-157, 164], trospium [155, 162, 165], tolterodine [166] and propiverine [155, 167] are established, effective and well tolerated treatments even in long-term use [154, 155, 168, 169]. Darifenacin [170, 171] and solifenacin [169, 172] have been evaluated in NDO secondary to SCI and MS [155, 170, 171, 173] with results similar to other antimuscarinic drugs. A pilot study using solifenacin in NDO due to PD showed an improvement in UI [174]. The relatively new drug, fesoterodine, an active metabolite of tolterodine, has also been introduced, even though to date there has been no published clinical evidence of its use in the treatment of neuro-urological disorders. Favourable results with the new drug imidafenacin have been reported [175].

Side effects: Controlled-release antimuscarinics have some minor side effects, e.g. dry mouth [176, 177]. It has been suggested that different ways of administration may help to reduce side effects. Moreover, imidafenacin has been safely used in neurological patients with no worsening of cognitive function [175].

Other agents

Beta-3-adrenergic receptor agonists have recently been introduced and evaluated in OAB, but clinical experience in neuro-urological patients is limited [178]. Studies on safety and effectiveness in NDO are ongoing [179]. Depending on the results of these studies, combined therapy with antimuscarinics may be an attractive option [180].

3.4.2.3.2 Drugs for voiding symptoms

Detrusor underactivity: Cholinergic drugs, such as bethanechol and distigmine, have been considered to enhance detrusor contractility and promote bladder emptying, but are not frequently used in clinical practice [181]. Only preclinical studies have documented the potential benefits of cannabinoid agonists on improving detrusor contractility when administered intravesically [182, 183]. Conversely, RCTs on the use of nabixinols, D-9-tetrahydrocannabinol or oral cannabis extract did not report any significant reduction of incontinence episodes in MS patients [184].

Decreasing bladder outlet resistance: α -blockers (e.g. tamsulosin, naftopidil and silodosin) seem to be effective for decreasing bladder outlet resistance, post-void residual and AD [185-187].

Increasing bladder outlet resistance: Several drugs have shown efficacy in selected cases of mild SUI, but there are no high-level evidence studies in neurological patients [119].

3.4.2.4 Recommendations for drug treatments

Recommendations	LE	GR
Use antimuscarinic therapy as the first-line medical treatment for neurogenic detrusor overactivity.	1a	A
Alternative routes of administration (i.e., transdermal or intravesical) of antimuscarinic agents may be used.	2	A
Maximise outcomes for neurogenic detrusor overactivity by considering a combination of antimuscarinic agents.	3	B
Prescribe α -blockers to decrease bladder outlet resistance.	1b	A
Do not prescribe parasympathomimetics for underactive detrusor.	1a	A
Do not prescribe drug treatment in neurogenic stress urinary incontinence.	4	A*

*Upgraded based on panel consensus.

3.4.2.5 Minimally invasive treatment

3.4.2.5.1 Catheterisation

Intermittent self- or third-party catheterisation [188, 189] is the preferred management for neuro-urological patients who cannot effectively empty their bladders [119]. Sterile IC, as originally proposed by Guttman and Frankel [188], significantly reduces the risk of UTI and bacteriuria [119, 190, 191], compared with clean IC introduced by Lapidus *et al.* [189]. However, it has not yet been established whether or not the incidence of UTI, other complications and user satisfaction are affected by either sterile or clean IC, coated or uncoated catheters or by any other strategy.

Sterile IC cannot be considered a routine procedure [119, 191]. Aseptic IC is an alternative to sterile IC [192].

Contributing factors to contamination are insufficient patient education and the inherently greater risk of UTI in neuro-urological patients [119, 193-197]. The average frequency of catheterisations per day is four to six times [198] and the catheter size most often used is between 12-16 Fr. In aseptic IC, an optimum frequency of five times showed a reduction of UTI [198]. Ideally, bladder volume at catheterisation should, as a rule, not exceed 400-500 mL.

Indwelling transurethral catheterisation and, to a lesser extent, suprapubic cystostomy are associated with a range of complications as well as an enhanced risk for UTI [119, 199-207]. Therefore, both procedures should be avoided, when possible. Silicone catheters are preferred as they are less susceptible to encrustation and because of the high incidence of latex allergy in the neuro-urological patient population [208].

3.4.2.5.2 Recommendations for catheterisation

Recommendations	LE	GR
Use intermittent catheterisation, whenever possible aseptic technique, as a standard treatment for patients who are unable to empty their bladder.	3	A
Thoroughly instruct patients in the technique and risks of intermittent catheterisation.	3	A
Use a catheter size between 12-16 Fr.	4	B*
Avoid indwelling transurethral and suprapubic catheterisation whenever possible.	3	A

*Upgraded based on panel consensus.

3.4.2.5.3 Intravesical drug treatment

To reduce DO, antimuscarinics can also be administered intravesically [209-213]. The efficacy, safety and tolerability of intravesical administration of 0.1% oxybutynin hydrochloride compared to its oral administration for treatment of NDO has been demonstrated in a recent randomised controlled study [213]. This approach may reduce adverse effects due to the fact that the antimuscarinic drug is metabolised differently [210] and a greater amount is sequestered in the bladder, even more than with electromotive administration [209].

The vanilloids, capsaicin and resiniferatoxin, desensitise the C-fibres and thereby decrease DO, for a period of a few months, until the sensation of these fibres has been restored [214-216]. The dosage is 1-2 mMol capsaicin in 100 mL 30% alcohol, or 10-100 nMol resiniferatoxin in 100 mL 10% alcohol for 30 minutes. Resiniferatoxin has about a 1,000-fold potency compared to capsaicin, with less pain during the instillation, and is effective in a patient refractory to capsaicin. Clinical studies have shown that resiniferatoxin has limited clinical efficacy compared to botulinum toxin A (BTX-A) injections in the detrusor [215]. Currently, there is no indication for the use of these substances, which are not licensed for intravesical treatment.

3.4.2.5.4 Botulinum toxin injections in the bladder

Botulinum toxin A causes a long-lasting but reversible chemical denervation that lasts for about nine months [217, 218]. The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. Botulinum toxin A has been proven effective in patients with neuro-urological disorders due to MS or SCI in phase III RCTs [219, 220] and systematic reviews [221, 222]. Repeated injections seem to be possible without loss of efficacy [217, 223, 224]. The most frequent side effects are UTIs and elevated PVR [220, 223]. Intermittent catheterisation may become necessary. Rare but severe adverse events include AD and respiratory problems. Generalised muscular weakness may occur [217, 220, 224].

3.4.2.5.5 Bladder neck and urethral procedures

Reduction of the bladder outlet resistance may be necessary to protect the UUT. This can be achieved by chemical denervation of the sphincter or by surgical interventions (bladder neck or sphincter incision or urethral stent). Incontinence may result and can be managed by external devices (see Section 3.4.2.1).

Botulinum toxin A: This can be used to treat DSD effectively by injection at a dose that depends on the preparation used. The dyssynergia is abolished for a few months, necessitating repeat injections. The efficacy of this treatment has been reported to be high and with few adverse effects [225-227]. However, a recent Cochrane report concluded that because of limited evidence future RCTs assessing the effectiveness of BTX-A injections also need to address the uncertainty about the optimal dose and mode of injection [228]. In addition, this therapy is not licensed.

Balloon dilatation: Favourable immediate results were reported [229], but there have been no further reports since 1994 therefore, this method is no longer recommended.

Sphincterotomy: By staged incision, bladder outlet resistance can be reduced without completely losing the closure function of the urethra [118, 119, 219]. Different techniques are used, and laser treatment appears to be advantageous [230, 231]. Sphincterotomy needs to be repeated at regular intervals in many patients [232], but it is efficient and does not cause severe adverse effects [118, 229]. Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered [233].

Bladder neck incision: This is indicated only for secondary changes at the bladder neck (fibrosis) [118, 230]. This procedure is not recommended in patients with detrusor hypertrophy, which causes thickening of the bladder neck [118].

Stents: Implantation of urethral stents results in continence being dependent on adequate closure of the bladder neck [119]. The results are comparable with sphincterotomy and the stenting procedure has a shorter duration of surgery and hospital stay [234, 235]. However, the costs [118], possible complications and re-interventions [236, 237] are limiting factors in their use [238-241].

Increasing bladder outlet resistance: This can improve the continence condition. Despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with neuro-urological disorders [119, 242, 243].

Urethral inserts: Urethral plugs or valves for the management of (female) stress incontinence have not been applied in neuro-urological patients. The experience with active pumping urethral prosthesis for treatment of the underactive or acontractile detrusor were disappointing [244].

3.4.2.5.6 Recommendations for minimal invasive treatment*

Recommendations	LE	GR
Use botulinum toxin injection in the detrusor to reduce neurogenic detrusor overactivity in multiple sclerosis or spinal cord injury patients if antimuscarinic therapy is ineffective.	1a	A
Bladder neck incision is effective in a fibrotic bladder neck.	4	B

*Recommendations for catheterisation are listed separately under Section 3.4.2.5.2.

3.4.3 Surgical treatment

3.4.3.1 Bladder neck and urethral procedures

Increasing the bladder outlet resistance has the inherent risk of causing high intravesical pressure. Procedures to treat sphincteric incontinence are therefore suitable only when the detrusor activity can be controlled and when no significant reflux is present. A simultaneous bladder augmentation and IC may be necessary [119].

Urethral sling: Various materials have been used for this procedure with enduring positive results. The procedure is established in women with the ability to self-catheterise [119, 245-250]. There is growing evidence that synthetic slings can be used effectively with acceptable medium to long-term results and minimal morbidity in neurological patients [251, 252]. Besides the pubovaginal sling, which has been considered the procedure of choice in this subgroup of patients, recent reports suggest that both the transobturator and the retropubic approaches may also be considered, with similar failure rates and a reduction in the need for IC. However, for both approaches a higher incidence of de novo urgency was reported [252, 253]. In men, both autologous and synthetic slings may also be an alternative [251, 252, 254-256].

Artificial urinary sphincter: This device was introduced by Light and Scott [257] for patients with neuro-urological disorders [119]. It has stood the test of time and acceptable long-term outcomes can be obtained [258-263].

Functional sphincter augmentation: Transposing the gracilis muscle to the bladder neck [264] or proximal urethra [265], can enable the possible creation of a functional autologous sphincter by electrical stimulation [264-266]. Therefore, raising the prospect of restoring control over the urethral closure.

Bladder neck and urethra reconstruction: The classical Young-Dees-Leadbetter procedure [267] for bladder neck reconstruction in children with bladder exstrophy, and Kropp urethra lengthening [268] improved by Salle [269], are established methods to restore continence provided that IC is practiced and/or bladder augmentation is performed [119, 270].

Urethral inserts: See section 3.4.2.5.5.

3.4.3.2 *Denervation, deafferentation, sacral neuromodulation*

Sacral rhizotomy, also known as sacral deafferentation, has achieved some success in reducing DO [271-273], but nowadays, it is used mostly as an adjuvant to sacral anterior root stimulation (SARS) [274-278]. Alternatives to rhizotomy are sought in this treatment combination [279-281].

Sacral anterior root stimulation is aimed at producing detrusor contraction. The technique was developed by Brindley [282] and is only applicable to complete lesions above the implant location, as its stimulation amplitude is over the pain threshold. The urethral sphincter efferents are also stimulated, but because the striated muscle relaxes faster than the smooth muscle of the detrusor, so-called “post-stimulus voiding” occurs. This approach has been successful in highly selected patients [275, 283, 284]. By changing the stimulation parameters, this method can also induce defecation or erection. A recent study reports that Charcot spinal arthropathy should be considered as a potential long-term complication of SARS, leading to spinal instability and to SARS dysfunction [285].

Sacral neuromodulation [286] might be effective and safe for treating neuro-urological symptoms, but there is a lack of RCTs and it is unclear which neurological patients are most suitable [287-290].

3.4.3.3 *Bladder covering by striated muscle*

When the bladder is covered by striated muscle that can be stimulated electrically, or ideally that can be contracted voluntarily, voiding function can be restored to an acontractile bladder. The rectus abdominis [291] and latissimus dorsi [292] have been used successfully in patients with neuro-urological symptoms [293, 294].

3.4.3.4 *Bladder augmentation*

The aim of auto-augmentation (detrusor myectomy) is to reduce DO or improve low bladder compliance. The advantages are: low surgical burden, low rate of long-term adverse effects, positive effect on patient QoL, and it does not preclude further interventions [118, 119, 295-301].

Replacing or expanding the bladder by intestine or other passive expandable coverage will improve bladder compliance and at least reduce the pressure effect of DO [302, 303]. Inherent complications associated with these procedures are: recurrent infection, stone formation, perforation or diverticula, possible malignant changes, and for the intestine, metabolic abnormality, mucus production and impaired bowel function [119, 304-306]. The procedure should be used with caution in patients with neuro-urological symptoms, but may become necessary if all less-invasive treatment methods have failed. Special attention should be paid to patients with pre-operative renal scars since metabolic acidosis can develop [307].

Bladder augmentation is a valid option to decrease detrusor pressure and increase bladder capacity, whenever more conservative approaches have failed. Several different techniques have been published, with comparable and satisfactory results [297, 308-316]. Bladder substitution, even by performing a supratrigonal cystectomy [317], to create a low-pressure reservoir is indicated in patients with a severely thick and fibrotic bladder wall [119]. Intermittent catheterisation may become necessary after this procedure. A significant improvement in QoL has been reported, probably related to the perception of better health and the resolution/improvement of urinary incontinence [318].

3.4.3.5 *Urinary diversion*

When no other therapy is successful, urinary diversion must be considered for the protection of the UUT and for the patient's QoL [119].

Continent diversion: This should be the first choice for urinary diversion. Patients with limited dexterity may prefer a stoma instead of using the urethra for catheterisation. A continent stoma can be created using various techniques. However, all of them have frequent complications, including leakage or stenosis. The short-term continence rates are > 80% and good protection of the UUT is achieved [119, 319-331]. For cosmetic reasons, the umbilicus is often used for the stoma site [326, 329, 330, 332-334].

Incontinent diversion: If catheterisation is impossible, incontinent diversion with a urine-collecting device is indicated. Ultimately, it could be considered in patients who are wheelchair bound or bed-ridden with intractable and untreatable incontinence, in patients with LUT destruction, when the UUT is severely compromised, and in patients who refuse other therapy [119]. An ileal segment is used for the deviation in most cases [119, 335-338]. Patients gain better functional status and QoL after surgery [339].

Undiversion: Long-standing diversions may be successfully undiverted or an incontinent diversion changed to a continent one with the emergence of new and better techniques for control of detrusor pressure and incontinence [119]. The patient must be carefully counselled and must comply meticulously with the instructions [119]. Successful undiversion can then be performed [340].

3.4.3.6 Recommendations for surgical treatment

Recommendations	LE	GR
Perform bladder augmentation in order to treat refractory neurogenic detrusor overactivity.	3	A
Place an autologous urethral sling in female patients with neurogenic stress urinary incontinence who are able to self-catheterise.	4	B*
Insert an artificial urinary sphincter in male patients with neurogenic stress urinary incontinence.	3	A

*Upgraded bases on panel consensus.

3.5 Urinary tract infection in neuro-urological patients

3.5.1 Epidemiology, aetiology and pathophysiology

Urinary tract infection is the onset of signs and/or symptoms accompanied by laboratory findings of a UTI (bacteriuria, leukocyturia and positive urine culture) [332]. There are no evidence-based cut-off values for the quantification of these findings. The published consensus is that a significant bacteriuria in persons performing IC is present with $> 10^2$ cfu/mL, $> 10^4$ cfu/mL in clean-void specimens and any detectable concentration in suprapubic aspirates. Regarding leukocyturia, 10 or more leukocytes in centrifuged urine samples per microscopic field (400x) are regarded as significant [332].

The pathogenesis of UTI in neuro-urological patients is multifactorial. Male gender seems to be a risk factor for febrile UTI [341]. Several etiological factors have been described: altered intrinsic defence mechanisms, impaired washout and catheterisation [342]. The exact working mechanisms, however, still remain unknown. The presence of asymptomatic bacteriuria in SCI patients is higher than in the general population, and varies depending on bladder management. Prevalence of bacteriuria in those performing clean IC varies from 23-89% [343]. Sphincterotomy and condom catheter drainage has a 57% prevalence [344]. Asymptomatic bacteria should not be routinely screened for in this population [345].

Individuals with neuro-urological symptoms, especially those with SCI, may have other signs and symptoms in addition to or instead of traditional signs and symptoms of a UTI in able-bodied individuals. Other problems, such as AD, may develop or worsen due to a UTI [346]. The most common signs and symptoms suspicious of a UTI in those with neuro-urological disorders are fever, new onset or increase in incontinence, including leaking around an indwelling catheter, increased spasticity, malaise, lethargy or sense of unease, cloudy urine with increased urine odour, discomfort or pain over the kidney or bladder, dysuria, or AD [346, 347].

3.5.2 Diagnostic evaluation

The gold standard for diagnosis is urine culture and urinalysis. A dipstick test may be more useful to exclude than to prove UTI [348, 349]. As bacterial strains and resistance patterns in persons with neuro-urological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory [350].

3.5.3 Disease management

Bacteriuria in patients with neuro-urological disorders should not be treated. Treatment of asymptomatic bacteriuria results in significantly more resistant bacterial strains without improving the outcome [351]. Urinary tract infections in persons with neuro-urological disorders are by definition a complicated UTI. Therefore, single-dose treatment is not advised. There is no consensus in the literature about the duration of treatment, it depends on the severity of the UTI and the involvement of kidneys and the prostate. Generally, a five to seven day course of antibiotic treatment is advised, which can be extended up to fourteen days according to the extent of the infection [351]. The choice of antibiotic therapy should be based on the results of the microbiologic testing. If immediate treatment is mandatory (e.g. fever, septicaemia, intolerable clinical

symptoms, extensive AD), the choice of treatment should be based on local and individual resistance profiles [352].

3.5.3.1 Recurrent UTI

Recurrent UTI in patients with neuro-urological disorders may indicate suboptimal management of the underlying functional problem, e.g. high bladder pressure during storage and voiding, incomplete voiding or bladder stones. The improvement of bladder function, by treating DO by BTX-A injection in the detrusor [353], and the removal of bladder stones or other direct supporting factors, especially indwelling catheters, as early as possible, are mandatory [350].

3.5.3.2 Prevention

If the improvement of bladder function and removal of foreign bodies/stones is not successful, additional UTI prevention strategies should be utilised. The use of hydrophilic catheters was associated with a lower rate of UTI in a recent meta-analysis [354]. Bladder irrigation has not been proven effective [355].

Various medical approaches have been tested for UTI prophylaxis in patients with neuro-urological disorders. The benefit of cranberry juice for the prevention of UTI could not be demonstrated in RCTs [356]. Methenamine hippurate is not effective in individuals with neuro-urological symptoms [357]. There is no sufficient evidence to support the use of L-methionine for urine acidification to prevent recurrent UTI [358]. There is only weak evidence that oral immunotherapy reduces bacteriuria in patients with SCI, and no evidence that recurrent UTIs are reduced [359]. Low-dose, long-term, antibiotic prophylaxis cannot reduce UTI frequency, but increases bacterial resistance and is therefore not recommended [351].

An application scheme of antibiotic substances for antibiotic prophylaxis provided long-term positive results, but the results of this trial need to be confirmed in further studies [360]. Another possible future option, the inoculation of apathogenic *Escherichia coli* strains into the bladder, has provided positive results in initial studies, but because of the paucity of data [361], cannot be recommended as a treatment option.

In summary, based on the criteria of evidence-based medicine, there is currently no preventive measure for recurrent UTI in patients with neuro-urological disorders that can be recommended without limitations. Therefore, individualised concepts should be taken into consideration, including immunostimulation, phytotherapy and complementary medicine [362]. Prophylaxis in patients with neuro-urological disorders is important to pursue, but since there are no data favouring one approach over another, prophylaxis is essentially a trial and error approach.

3.5.4 Recommendations for the treatment of UTI

Recommendations	LE	GR
Do not screen for or treat asymptomatic bacteriuria in patients with neuro-urological disorders.	4	A*
Avoid the use of long-term antibiotics for recurrent urinary tract infections (UTIs).	2a	A
In patients with recurrent UTI, optimise treatment of neuro-urological symptoms and remove foreign bodies (e.g. stones, indwelling catheters) from the urinary tract.	3	A
In patients with neuro-urological disorders, UTI prophylaxis must be individualised since there is no optimal prophylactic measure available.	4	C

*Upgraded based on panel consensus.

3.6 Sexual (dys)function and fertility

These Guidelines specifically focus on sexual dysfunction and infertility in patients with a neurological disease [363, 364]. Non-neurogenic, male sexual dysfunction and infertility are covered in separate EAU Guidelines [365, 366]. In neuro-urological patients sexual problems can be identified at three levels: primary (direct neurological damage), secondary (general physical disabilities) and tertiary (psychosocial and emotional issues) sexual dysfunction [367]. Adopting a systematic approach, such as the PLISSIT model (Permission, Limited Information, Specific Suggestions and Intensive Therapy) [368], provides a framework for counselling and treatment involving a stepwise approach to the management of neurogenic sexual dysfunction. Sexual dysfunction is associated with neurogenic lower urinary tract dysfunction in patients with MS [369] and spina bifida [370]. Although various patient-reported outcome measures (PROMs) are available to evaluate sexual function, the evidence for good PROMs is limited and studies with high methodological quality are needed [371].

3.6.1 **Erectile dysfunction (ED)**

3.6.1.1 *Phosphodiesterase type 5 inhibitors (PDE5Is)*

Questions:

- What is the effectiveness of the various PDE5Is in the different neuro-urological patient groups?
- What common side-effects are described?

Evidence:

Phosphodiesterase type 5 inhibitors (PDE5Is) are recommended as first-line treatment in neurogenic erectile dysfunction (ED) [363, 372]. In SCI patients, tadalafil, vardenafil and sildenafil have all improved retrograde ejaculation and improved erectile function and satisfaction on IIEF-15. Tadalafil 10 mg was shown to be more effective than sildenafil 50 mg. All currently available PDE5Is appear to be effective and safe, although there are no high level evidence studies in neuro-urological patients investigating the efficacy and side effects across different PDE5Is, dosages and formulations [373].

For MS patients two studies reported significant improvement in ED when using sildenafil and tadalafil. One study, however, showed no improvement in ED with sildenafil.

In PD normal erectile function was described in over half of the patients using sildenafil 100 mg and a significant improvement in IIEF-15 score was found compared to placebo. While most neuro-urological patients require long-term therapy for ED some have a low compliance rate or stop therapy because of side effects [374, 375], most commonly headache and flushing [372]. In addition, PDE5Is may induce relevant hypotension in patients with tetraplegia/high-level paraplegia and multiple system atrophy [374, 375]. As a prerequisite for successful PDE5I-therapy, some residual nerve function is required to induce erection. Since many patients with SCI use on-demand nitrates for the treatment of AD, they must be counselled that PDE5Is are contraindicated when using nitrate medication.

3.6.1.2 *Drug therapy other than PDE5Is*

Fampridine to treat neurogenic spasticity has been shown to be beneficial in improving ED in two domains of the IIEF-15 in SCI and MS patients, however, with a significant discontinuation rate due to severe adverse events [376]. Sublingual apomorphine was shown to have poor results on ED in SCI patients and side-effects in half of the patients [377]. In PD pergolide mesylate showed a significant improvement in IIEF-15 scores up to twelve months follow-up [378].

3.6.1.3 *Mechanical devices*

Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular [379-383].

3.6.1.4 *Intracavernous injections and intraurethral application*

Patients not responding to oral drugs may be offered intracavernous injections (alprostadil, papaverine and phentolamine) that have been shown to be effective in a number of neurological conditions, including SCI, MS, and diabetes mellitus [384-390] but their use requires careful dose titration and some precautions. Complications of intracavernous drugs include pain, priapism and corpora cavernosa fibrosis.

Intracavernous vasoactive drug injection is the first-line therapeutic option in patients taking nitrate medications, as well as those with concerns about drug interactions with PDE5Is, or in whom PDE5Is are ineffective. The impact of intracavernous injections on ejaculation and orgasmic function, their early use for increasing the recovery rate of a spontaneous erection, and their effectiveness and tolerability in the long-term are unclear [374]. Intraurethral alprostadil application is an alternative but a less effective route of administration [390, 391].

3.6.1.5 *Sacral neuromodulation*

Sacral neuromodulation for LUT dysfunction may improve sexual function but high level evidence studies are lacking [372].

3.6.1.6 *Penile prostheses*

Penile prostheses may be considered for treatment of neurogenic ED when all conservative treatments have failed. At a mean follow-up of seven years 83.7% of patients with SCI were able to have sexual intercourse [372]. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type [392-394].

3.6.1.7 *Recommendations for erectile dysfunction*

Recommendations	LE	GR
Prescribe oral phosphodiesterase type 5 inhibitors as first-line medical treatment in neurogenic erectile dysfunction.	1b	A
Give intracavernous injections of vasoactive drugs (alone or in combination) as second-line medical treatment in neurogenic erectile dysfunction.	3	A
Offer mechanical devices such as vacuum devices and rings to patients with neurogenic erectile dysfunction.	3	B
Reserve penile prostheses for selected patients with neurogenic erectile dysfunction.	4	B*

*Upgraded based on panel consensus.

3.6.2 **Male fertility**

Male fertility can be compromised in the neurological patient by ED, ejaculation disorder, impaired sperm quality or various combinations of these three disorders. Among the major conditions contributing to neurogenic infertility are pelvic and retroperitoneal surgery, diabetes mellitus, SB, MS and SCI [395]. Erectile dysfunction is managed as described previously. Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck, including imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine [395]. The use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation [396]. If antegrade ejaculation is not achieved, the harvest of semen from the urine may be considered [397].

Prostatic massage is safe and easy to use for obtaining semen in men with lesions above Th 10 [398]. In several patients, vibrostimulation or transrectal electroejaculation are needed for sperm retrieval [390, 395, 399, 400]. Semen retrieval is more likely with vibrostimulation in men with lesions above Th 10 [401-403]. In men with SCI, especially at or above Th 6, AD might occur during sexual activity and ejaculation [404, 405]; patients at risk and fertility clinics must be informed and aware of this potentially life-threatening condition. In SCI patients the use of oral midodrine can improve sperm retrieval at vibrostimulation [406].

In men with MS, use of disease modifying drugs during the conception phase, has not been associated with altered pregnancy outcomes [407]. Surgical procedures, such as, microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE), may be used if vibrostimulation and electroejaculation are not successful [408, 409]. Pregnancy rates in patients with SCI are lower than in the general population, but since the introduction of intracytoplasmic sperm injection (ICSI), men with SCI now have a good chance of becoming biological fathers [410-412].

3.6.2.1 *Sperm quality and motility*

The following has been reported on sperm quality and motility:

- bladder management with clean IC may improve semen quality compared to indwelling catheterisation, reflex voiding or bladder expression [413];
- in SCI patients sperm quality decreases at the early post traumatic phase demonstrating lower spermatozoid vitality (necrospermia), reduced motility (asthenospermia) and leucospermia [408];
- long-term valproate treatment for epilepsy negatively influences sperm count and motility [414];
- vibrostimulation produces samples with better sperm motility than electrostimulation [415, 416];
- electroejaculation with interrupted current produces better sperm motility than continuous current [417];
- freezing of sperm is unlikely to improve fertility rates in men with SCI [418].

3.6.2.2 *Recommendations for male fertility*

Recommendations	LE	GR
Perform vibrostimulation and transrectal electroejaculation for sperm retrieval in men with spinal cord injury.	3	B
Perform microsurgical epididymal sperm aspiration, testicular sperm extraction and intracytoplasmic sperm injection after failed vibrostimulation and/or transrectal electroejaculation in men with spinal cord injury.	3	B
Counsel men with spinal cord injury at or above Th 6 and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	3	A*

*Upgraded based on panel consensus.

3.6.3 **Female sexuality**

The most relevant publications on neurogenic female sexual dysfunction are in women with SCI and MS. After SCI, about 65-80% of women continue to be sexually active, but to a much lesser extent than before the injury, and about 25% report a decreased satisfaction with their sexual life [419-421]. Although sexual dysfunction is very common in women with MS, it is still often overlooked by medical professionals [422, 423].

The greatest physical barrier to sexual activity is UI. A correlation has been found between the urodynamic outcomes of low bladder capacity, compliance and high maximum detrusor pressure and sexual dysfunction in MS patients. Problems with positioning and spasticity affect mainly tetraplegic patients. Peer support may help to optimise the sexual adjustment of women with SCI in achieving a more positive self-image, self-esteem and feelings of being attractive to themselves and others [419, 424-426].

The use of specific drugs for sexual dysfunction is indicated to treat inadequate lubrication. Data on sildenafil for treating female sexual dysfunction are poor and controversial [427]. Although good evidence exists that psychological interventions are effective in the treatment of female hypoactive sexual desire disorder and female orgasmic disorder [428], there is a lack of high-evidence level studies in the neurological population.

Neurophysiological studies have shown that women with the ability to perceive Th 11-L2 pin-prick sensations may have psychogenic genital vasocongestion. Reflex lubrication and orgasm is more prevalent in women with SCI who have preserved the sacral reflex arc (S2-S5), even when it has not been shown in an individual woman that a specific level and degree of lesion is the cause of a particular sexual dysfunction. In SCI women with a complete lesion of the sacral reflex, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions [429-431].

Sacral neuromodulation for LUT dysfunction may improve sexual function but high-evidence studies are lacking [427].

Women with SCI reported dissatisfaction with the quality and quantity of sexuality-related rehabilitation services and were less likely to receive sexual information than men [429, 432, 433].

3.6.3.1 *Recommendation for female sexuality*

Recommendation	LE	GR
Do not offer medical therapy for the treatment of neurogenic sexual dysfunction in women.	4	A*

*Upgraded based on panel consensus.

3.6.4 **Female fertility**

There are few studies on female fertility in neurological patients. More than a third (38%) of women with epilepsy had infertility and the relevant predictors were exposure to multiple (three or more) antiepileptic drugs, older age and lower education [434].

Although it seems that the reproductive capacity of women with SCI is only temporarily affected by SCI with cessation of menstruation for approximately six months after SCI [435], there are no high-evidence level studies. About 70% of sexually active women use some form of contraception after injury, but fewer women use the birth control pill compared to before their injury [436].

Women with SCI are more likely to suffer complications during pregnancy, labour and delivery compared to able-bodied women. Complications of labour and delivery include bladder problems, spasticity, pressure sores, anaemia, and AD [437, 438]. Obstetric outcomes include higher rates of Caesarean sections and an increased incidence of low birth-weight babies [436].

Epidural anaesthesia is chosen and effective for most patients with AD during labour and delivery [439, 440].

There is very little published data on women's experience of the menopause following SCI [441]. Women with MS who plan a pregnancy should evaluate their current drug treatment with their treating physician [442]. Clinical management should be individualised to optimise both the mother's reproductive outcomes and MS course [443].

3.6.4.1 Recommendation for female fertility

Recommendation	LE	GR
Take a multidisciplinary approach, tailored to individual patient's needs and preferences, in the management of fertility, pregnancy and delivery in women with neurological diseases.	4	A*

*Upgraded based on panel consensus.

3.7 Follow-up

3.7.1 Introduction

Neuro-urological disorders are often unstable and the symptoms may vary considerably, even within a relatively short period. Regular follow-up is therefore necessary [117].

Depending on the type of the underlying neurological pathology and the current stability of the neuro-urological symptoms, the interval between initial investigations and control diagnostics may vary and in many cases should not exceed one to two years. In high-risk neuro-urological patients this interval should be much shorter. Urinalysis should be performed regularly; the frequency to be guided by patient symptoms. The UUT should be checked by ultrasonography at regular intervals in high-risk patients; about once every six months. In these patients, physical examination and urine laboratory should take place every year. Any significant clinical change warrants further, specialised, investigation. However, there is a complete lack of high level evidence studies on this topic and every recommendation must be viewed critically in each individual neuro-urological patient [117].

In addition, bladder wall thickness can be measured on ultrasonography as an additional risk assessment for upper tract damage [444], although a 'safe' cut-off threshold for this has not been agreed [445]. The utility of DMSA for follow-up of neuro-urological patients has not been fully evaluated [446].

3.7.2 Recommendations for follow-up

Recommendations	LE	GR
Assess the upper urinary tract at regular intervals in high risk patients.	4	A*
Perform a physical examination and urine laboratory every year in high risk patients.	4	A*
Any significant clinical changes should instigate further, specialised, investigation.	4	A*
Perform urodynamic investigation as a mandatory baseline diagnostic intervention in high-risk patients at regular intervals.	3	A

*Upgraded based on panel consensus.

3.8 Conclusions

Neuro-urological disorders have a multi-faceted pathology. They require an extensive and specific diagnosis before one can embark on an individualised therapy, which takes into account the medical and physical condition of the patient and the patient's expectations about their future. The urologist can select from a wealth of therapeutic options, each with its own pros and cons. Notwithstanding the success of any therapy embarked upon, close surveillance is necessary for the patient's entire life.

These Guidelines offer you expert advice on how to define the patient's neuro-urological symptoms as precisely as possible and how to select, together with the patient, the appropriate therapy. This last choice, as always, is governed by the golden rule: as effective as needed, as non-invasive as possible.

4. REFERENCES

- Schafer, W., *et al.* Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. *Neurourol Urodyn*, 2002. 21: 261.
<https://www.ncbi.nlm.nih.gov/pubmed/11948720>
- Abrams, P., *et al.* Reviewing the ICS 2002 terminology report: the ongoing debate. *Neurourol Urodyn*, 2009. 28: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/19350662>

3. Abrams, P., *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*, 2002. 21: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/11857671>
4. Groen, J., *et al.* Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. *Eur Urol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26304502>
5. Nosseir, M., *et al.* Clinical usefulness of urodynamic assessment for maintenance of bladder function in patients with spinal cord injury. *Neurourol Urodyn*, 2007. 26: 228.
<https://www.ncbi.nlm.nih.gov/pubmed/16998859>
6. Panicker, J.N., *et al.* Lower urinary tract dysfunction in the neurological patient: clinical assessment and management. *Lancet Neurol*, 2015. 14: 720.
<https://www.ncbi.nlm.nih.gov/pubmed/26067125>
7. Phe, V., *et al.* Continent catheterizable tubes/stomas in adult neuro-urological patients: A systematic review. *Neurourol Urodyn*, 2017. DOI: 10.1002/nau.23213
<https://www.ncbi.nlm.nih.gov/pubmed/28139848>
8. Ecclestone, H., *et al.* Long term effectiveness and complication rate of bladder reconstruction and urinary diversions in patients with neuropathic bladder dysfunction. PROSPERO 2015. CRD42015015762.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015762
9. Phillips B, *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
10. Townsend, N., *et al.* Cardiovascular disease in Europe - epidemiological update 2015. *Eur Heart J*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26306399>
11. Tibaek, S., *et al.* Prevalence of lower urinary tract symptoms (LUTS) in stroke patients: a cross-sectional, clinical survey. *Neurourol Urodyn*, 2008. 27: 763.
<https://www.ncbi.nlm.nih.gov/pubmed/18551565>
12. Marinkovic, S.P., *et al.* Voiding and sexual dysfunction after cerebrovascular accidents. *J Urol*, 2001. 165: 359.
<https://www.ncbi.nlm.nih.gov/pubmed/11176374>
13. Rotar, M., *et al.* Stroke patients who regain urinary continence in the first week after acute first-ever stroke have better prognosis than patients with persistent lower urinary tract dysfunction. *Neurourol Urodyn*, 2011. 30: 1315.
<https://www.ncbi.nlm.nih.gov/pubmed/21488096>
14. Lobo, A., *et al.* Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology*, 2000. 54: S4.
<https://www.ncbi.nlm.nih.gov/pubmed/10854354>
15. Na, H.R., *et al.* Urinary incontinence in Alzheimer's disease is associated with Clinical Dementia Rating-Sum of Boxes and Barthel Activities of Daily Living. *Asia Pac Psychiatry*, 2015. 7: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/23857871>
16. Grant, R.L., *et al.* First diagnosis and management of incontinence in older people with and without dementia in primary care: a cohort study using The Health Improvement Network primary care database. *PLoS Med*, 2013. 10: 1001.
<https://www.ncbi.nlm.nih.gov/pubmed/24015113>
17. Pringsheim, T., *et al.* The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*, 2014. 29: 1583.
<https://www.ncbi.nlm.nih.gov/pubmed/24976103>
18. Ragab, M.M., *et al.* Idiopathic Parkinson's disease patients at the urologic clinic. *Neurourol Urodyn*, 2011. 30: 1258.
<https://www.ncbi.nlm.nih.gov/pubmed/21404318>
19. Papatsoris, A.G., *et al.* Urinary and erectile dysfunction in multiple system atrophy (MSA). *Neurourol Urodyn*, 2008. 27: 22.
<https://www.ncbi.nlm.nih.gov/pubmed/17563111>
20. Kim, M., *et al.* Impaired detrusor contractility is the pathognomonic urodynamic finding of multiple system atrophy compared to idiopathic Parkinson's disease. *Parkinsonism Relat Disord*, 2015. 21: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/25534084>

21. Sakakibara, R., *et al.* A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. *Neurourol Urodyn*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25810035>
22. Dolecek, T.A., *et al.* CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol*, 2012. 14 Suppl 5: v1.
<https://www.ncbi.nlm.nih.gov/pubmed/23095881>
23. Maurice-Williams, R.S. Micturition symptoms in frontal tumours. *J Neurol Neurosurg Psychiatry*, 1974. 37: 431.
<https://www.ncbi.nlm.nih.gov/pubmed/4365244>
24. Christensen, D., *et al.* Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning - Autism and Developmental Disabilities Monitoring Network, USA, 2008. *Dev Med Child Neurol*, 2014. 56: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/24117446>
25. Marciniak, C., *et al.* Urinary incontinence in adults with cerebral palsy: prevalence, type, and effects on participation. *PM R*, 2014. 6: 110.
<https://www.ncbi.nlm.nih.gov/pubmed/23978464>
26. Tagliaferri, F., *et al.* A systematic review of brain injury epidemiology in Europe. *Acta Neurochir (Wien)*, 2006. 148: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/16311842>
27. Kulakli, F., *et al.* Relationship between urinary dysfunction and clinical factors in patients with traumatic brain injury. *Brain Inj*, 2014. 28: 323.
<https://www.ncbi.nlm.nih.gov/pubmed/24377376>
28. Singh, A., *et al.* Global prevalence and incidence of traumatic spinal cord injury. *Clin Epidemiol*, 2014. 6: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/25278785>
29. Weld, K.J., *et al.* Association of level of injury and bladder behavior in patients with post-traumatic spinal cord injury. *Urology*, 2000. 55: 490.
<https://www.ncbi.nlm.nih.gov/pubmed/10736489>
30. Kondo, A., *et al.* Neural tube defects: prevalence, etiology and prevention. *Int J Urol*, 2009. 16: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/19120526>
31. Sawin, K.J., *et al.* The National Spina Bifida Patient Registry: profile of a large cohort of participants from the first 10 clinics. *J Pediatr*, 2015. 166: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/25444012>
32. Bartolin, Z., *et al.* Relationship between clinical data and urodynamic findings in patients with lumbar intervertebral disk protrusion. *Urol Res*, 2002. 30: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/12202938>
33. Lange, M.M., *et al.* Urinary and sexual dysfunction after rectal cancer treatment. *Nat Rev Urol*, 2011. 8: 51.
<https://www.ncbi.nlm.nih.gov/pubmed/21135876>
34. IDF Diabetes Atlas, 7th edn. 2015, International Diabetes Federation: Brussels, Belgium.
<http://www.diabetesatlas.org/>
35. Yuan, Z., *et al.* Diabetic cystopathy: A review. *J Diabetes*, 2015. 7: 442.
<https://www.ncbi.nlm.nih.gov/pubmed/25619174>
36. Pugliatti, M., *et al.* The epidemiology of multiple sclerosis in Europe. *Eur J Neurol*, 2006. 13: 700.
<https://www.ncbi.nlm.nih.gov/pubmed/16834700>
37. de Seze, M., *et al.* The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. *Mult Scler*, 2007. 13: 915.
<https://www.ncbi.nlm.nih.gov/pubmed/17881401>
38. Krassioukov, A., *et al.* International standards to document remaining autonomic function after spinal cord injury. *J Spinal Cord Med*, 2012. 35: 201.
<https://www.ncbi.nlm.nih.gov/pubmed/22925746>
39. Irwin, D.E., *et al.* Understanding the elements of overactive bladder: questions raised by the EPIC study. *BJU Int*, 2008. 101: 1381.
<https://www.ncbi.nlm.nih.gov/pubmed/18336602>
40. Fix, J.D., *Neuroanatomy*. 4th ed. 2008, Philadelphia, Pennsylvania, USA.
41. Maynard, F.M., Jr., *et al.* International Standards for Neurological and Functional Classification of Spinal Cord Injury. American Spinal Injury Association. *Spinal Cord*, 1997. 35: 266.
<https://www.ncbi.nlm.nih.gov/pubmed/9160449>

42. Klevmark, B. Natural pressure-volume curves and conventional cystometry. *Scand J Urol Nephrol Suppl*, 1999. 201: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/10573769>
43. Del Popolo, G., *et al.* Diagnosis and therapy for neurogenic bladder dysfunctions in multiple sclerosis patients. *Neurol Sci*, 2008. 29 Suppl 4: S352.
<https://www.ncbi.nlm.nih.gov/pubmed/19089675>
44. Satar, N., *et al.* The effects of delayed diagnosis and treatment in patients with an occult spinal dysraphism. *J Urol*, 1995. 154: 754.
<https://www.ncbi.nlm.nih.gov/pubmed/7609171>
45. Watanabe, T., *et al.* High incidence of occult neurogenic bladder dysfunction in neurologically intact patients with thoracolumbar spinal injuries. *J Urol*, 1998. 159: 965.
<https://www.ncbi.nlm.nih.gov/pubmed/9474194>
46. Ahlberg, J., *et al.* Neurological signs are common in patients with urodynamically verified "idiopathic" bladder overactivity. *Neurourol Urodyn*, 2002. 21: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/11835426>
47. Bemelmans, B.L., *et al.* Evidence for early lower urinary tract dysfunction in clinically silent multiple sclerosis. *J Urol*, 1991. 145: 1219.
<https://www.ncbi.nlm.nih.gov/pubmed/2033697>
48. Klausner, A.P., *et al.* The neurogenic bladder: an update with management strategies for primary care physicians. *Med Clin North Am*, 2011. 95: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/21095415>
49. Bors, E., *et al.* History and physical examination in neurological urology. *J Urol*, 1960. 83: 759.
<https://www.ncbi.nlm.nih.gov/pubmed/13802958>
50. Cameron, A.P., *et al.* The Severity of Bowel Dysfunction in Patients with Neurogenic Bladder. *J Urol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25956470>
51. Vodusek, D.B. Lower urinary tract and sexual dysfunction in neurological patients. *Eur Neurol*, 2014. 72: 109.
<https://www.ncbi.nlm.nih.gov/pubmed/24993182>
52. Linsenmeyer, T.A., *et al.* Accuracy of individuals with spinal cord injury at predicting urinary tract infections based on their symptoms. *J Spinal Cord Med*, 2003. 26: 352.
<https://www.ncbi.nlm.nih.gov/pubmed/14992336>
53. Massa, L.M., *et al.* Validity, accuracy, and predictive value of urinary tract infection signs and symptoms in individuals with spinal cord injury on intermittent catheterization. *J Spinal Cord Med*, 2009. 32: 568.
<https://www.ncbi.nlm.nih.gov/pubmed/20025153>
54. Bellucci, C.H.S., *et al.* Acute spinal cord injury - Do ambulatory patients need urodynamic investigations? *J Urol*, 2013. 189: 1369.
<https://www.ncbi.nlm.nih.gov/pubmed/23069382>
55. Honjo, H., *et al.* Impact of convenience void in a bladder diary with urinary perception grade to assess overactive bladder symptoms: a community-based study. *Neurourol Urodyn*, 2010. 29: 1286.
<https://www.ncbi.nlm.nih.gov/pubmed/20878998>
56. Naoemova, I., *et al.* Reliability of the 24-h sensation-related bladder diary in women with urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*, 2008. 19: 955.
<https://www.ncbi.nlm.nih.gov/pubmed/18235981>
57. Henze, T. Managing specific symptoms in people with multiple sclerosis. *Int MS J*, 2005. 12: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/16417816>
58. Liu, C.W., *et al.* The relationship between bladder management and health-related quality of life in patients with spinal cord injury in the UK. *Spinal Cord*, 2010. 48: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/19841636>
59. Khalaf, K.M., *et al.* The impact of lower urinary tract symptoms on health-related quality of life among patients with multiple sclerosis. *Neurourol Urodyn*, 2016. 35: 48.
<https://www.ncbi.nlm.nih.gov/pubmed/25327401>
60. Pannek, J., *et al.* Does optimizing bladder management equal optimizing quality of life? Correlation between health-related quality of life and urodynamic parameters in patients with spinal cord lesions. *Urology*, 2009. 74: 263.
<https://www.ncbi.nlm.nih.gov/pubmed/19428089>
61. Patel, D.P., *et al.* Patient reported outcomes measures in neurogenic bladder and bowel: A systematic review of the current literature. *Neurourol Urodyn*, 2014.
<https://www.ncbi.nlm.nih.gov/pubmed/25327455>

62. Bonniaud, V., *et al.* Qualiveen, a urinary-disorder specific instrument: 0.5 corresponds to the minimal important difference. *J Clin Epidemiol*, 2008. 61: 505.
<https://www.ncbi.nlm.nih.gov/pubmed/18394545>
63. Bonniaud, V., *et al.* Development and validation of the short form of a urinary quality of life questionnaire: SF-Qualiveen. *J Urol*, 2008. 180: 2592.
<https://www.ncbi.nlm.nih.gov/pubmed/18950816>
64. Bonniaud, V., *et al.* Italian version of Qualiveen-30: cultural adaptation of a neurogenic urinary disorder-specific instrument. *Neurourol Urodyn*, 2011. 30: 354.
<https://www.ncbi.nlm.nih.gov/pubmed/21305589>
65. Ciudin, A., *et al.* Quality of life of multiple sclerosis patients: translation and validation of the Spanish version of Qualiveen. *Neurourol Urodyn*, 2012. 31: 517.
<https://www.ncbi.nlm.nih.gov/pubmed/22396437>
66. D'Ancona, C.A., *et al.* Quality of life of neurogenic patients: translation and validation of the Portuguese version of Qualiveen. *Int Urol Nephrol*, 2009. 41: 29.
<https://www.ncbi.nlm.nih.gov/pubmed/18528780>
67. Pannek, J., *et al.* [Quality of life in German-speaking patients with spinal cord injuries and bladder dysfunctions. Validation of the German version of the Qualiveen questionnaire]. *Urologe A*, 2007. 46: 1416.
<https://www.ncbi.nlm.nih.gov/pubmed/17605119>
68. Welk, B., *et al.* The conceptualization and development of a patient-reported neurogenic bladder symptom score. *Res Rep Urol*, 2013. 5: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/24400244>
69. Gulick, E.E. Bowel management related quality of life in people with multiple sclerosis: psychometric evaluation of the QoL-BM measure. *Int J Nurs Stud*, 2011. 48: 1066.
<https://www.ncbi.nlm.nih.gov/pubmed/21377677>
70. Tsang, B., *et al.* A systematic review and comparison of questionnaires in the management of spinal cord injury, multiple sclerosis and the neurogenic bladder. *Neurourol Urodyn*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25620137>
71. Schurch, B., *et al.* Reliability and validity of the Incontinence Quality of Life questionnaire in patients with neurogenic urinary incontinence. *Arch Phys Med Rehabil*, 2007. 88: 646.
<https://www.ncbi.nlm.nih.gov/pubmed/17466735>
72. Hollingworth, W., *et al.* Exploring the impact of changes in neurogenic urinary incontinence frequency and condition-specific quality of life on preference-based outcomes. *Qual Life Res*, 2010. 19: 323.
<https://www.ncbi.nlm.nih.gov/pubmed/20094804>
73. Patel, D.P., *et al.* Patient reported outcomes measures in neurogenic bladder and bowel: A systematic review of the current literature. *Neurourol Urodyn*, 2016. 35: 8.
<https://www.ncbi.nlm.nih.gov/pubmed/25327455>
74. Cella, D.F., *et al.* Validation of the functional assessment of multiple sclerosis quality of life instrument. *Neurology*, 1996. 47: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/8710066>
75. Wesson, J.M., *et al.* The functional index for living with multiple sclerosis: development and validation of a new quality of life questionnaire. *Mult Scler*, 2009. 15: 1239.
<https://www.ncbi.nlm.nih.gov/pubmed/19737850>
76. Gold, S.M., *et al.* Disease specific quality of life instruments in multiple sclerosis: validation of the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS). *Mult Scler*, 2001. 7: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/11424632>
77. Goodin, D.S. A questionnaire to assess neurological impairment in multiple sclerosis. *Mult Scler*, 1998. 4: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/9839306>
78. Foley, F.W., *et al.* The Multiple Sclerosis Intimacy and Sexuality Questionnaire -- re-validation and development of a 15-item version with a large US sample. *Mult Scler*, 2013. 19: 1197.
<https://www.ncbi.nlm.nih.gov/pubmed/>
79. Sanders, A.S., *et al.* The Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19). *Sexuality and Disability*, 2000. 18: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/23369892>
80. Marrie, R.A., *et al.* Validity and reliability of the MSQLI in cognitively impaired patients with multiple sclerosis. *Mult Scler*, 2003. 9: 621.
<https://www.ncbi.nlm.nih.gov/pubmed/14664477>

81. Vickrey, B.G., *et al.* A health-related quality of life measure for multiple sclerosis. *Qual Life Res*, 1995. 4: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/7613530>
82. Honan, C.A., *et al.* The multiple sclerosis work difficulties questionnaire (MSWDQ): development of a shortened scale. *Disabil Rehabil*, 2014. 36: 635.
<https://www.ncbi.nlm.nih.gov/pubmed/23786346>
83. Welk, B., *et al.* The validity and reliability of the neurogenic bladder symptom score. *J Urol*, 2014. 192: 452.
<https://www.ncbi.nlm.nih.gov/pubmed/24518764>
84. Bonniaud, V., *et al.* Measuring quality of life in multiple sclerosis patients with urinary disorders using the Qualiveen questionnaire. *Arch Phys Med Rehabil*, 2004. 85: 1317.
<https://www.ncbi.nlm.nih.gov/pubmed/15295759>
85. Franceschini, M., *et al.* Follow-up in persons with traumatic spinal cord injury: questionnaire reliability. *Eura Medicophys*, 2006. 42: 211.
<https://www.ncbi.nlm.nih.gov/pubmed/17039217>
86. Noreau, L., *et al.* Development and assessment of a community follow-up questionnaire for the Rick Hansen spinal cord injury registry. *Arch Phys Med Rehabil*, 2013. 94: 1753.
<https://www.ncbi.nlm.nih.gov/pubmed/23529142>
87. Liu, N., *et al.* Autonomic dysreflexia severity during urodynamics and cystoscopy in individuals with spinal cord injury. *Spinal Cord*, 2013. 51: 863.
<https://www.ncbi.nlm.nih.gov/pubmed/24060768>
88. Liu, N., *et al.* Iatrogenic urological triggers of autonomic dysreflexia: a systematic review. *Spinal Cord*, 2015. 53: 500.
<https://www.ncbi.nlm.nih.gov/pubmed/25800696>
89. Labat, J.J., *et al.* Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). *Neurourol Urodyn*, 2008. 27: 306.
<https://www.ncbi.nlm.nih.gov/pubmed/17828787>
90. Brown, D., *Atlas of regional anesthesia*. 3rd. ed. 2006, Philadelphia
91. Standring, S., *Gray's anatomy* . 40th ed. 2008.
92. Bellucci, C.H., *et al.* Neurogenic lower urinary tract dysfunction--do we need same session repeat urodynamic investigations? *J Urol*, 2012. 187: 1318.
<https://www.ncbi.nlm.nih.gov/pubmed/22341264>
93. Walter, M., *et al.* Autonomic dysreflexia and repeatability of cardiovascular changes during same session repeat urodynamic investigation in women with spinal cord injury. *World J Urol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26055644>
94. Gammie, A., *et al.* International Continence Society guidelines on urodynamic equipment performance. *Neurourol Urodyn*, 2014. 33: 370.
<https://www.ncbi.nlm.nih.gov/pubmed/24390971>
95. McGuire, E.J., *et al.* Leak-point pressures. *Urol Clin North Am*, 1996. 23: 253.
<https://www.ncbi.nlm.nih.gov/pubmed/8659025>
96. Ozkan, B., *et al.* Which factors predict upper urinary tract deterioration in overactive neurogenic bladder dysfunction? *Urology*, 2005. 66: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/15992868>
97. Wang, Q.W., *et al.* Is it possible to use urodynamic variables to predict upper urinary tract dilatation in children with neurogenic bladder-sphincter dysfunction? *BJU Int*, 2006. 98: 1295.
<https://www.ncbi.nlm.nih.gov/pubmed/17034510>
98. Linsenmeyer, T.A., *et al.* The impact of urodynamic parameters on the upper tracts of spinal cord injured men who void reflexly. *J Spinal Cord Med*, 1998. 21: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/9541882>
99. McGuire, E.J., *et al.* Prognostic value of urodynamic testing in myelodysplastic patients. *J Urol*, 1981. 126: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/7196460>
100. Krongrad, A., *et al.* Bladder neck dysynergia in spinal cord injury. *Am J Phys Med Rehabil*, 1996. 75: 204.
<https://www.ncbi.nlm.nih.gov/pubmed/8663928>
101. Weld, K.J., *et al.* Clinical significance of detrusor sphincter dyssynergia type in patients with post-traumatic spinal cord injury. *Urology*, 2000. 56: 565.
<https://www.ncbi.nlm.nih.gov/pubmed/11018603>

102. Rossier, A.B., *et al.* 5-microtransducer catheter in evaluation of neurogenic bladder function. *Urology*, 1986. 27: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/3962062>
103. Al-Ali, M., *et al.* A 10 year review of the endoscopic treatment of 125 spinal cord injured patients with vesical outlet obstruction: does bladder neck dyssynergia exist? *Paraplegia*, 1996. 34: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/8848321>
104. Bacsu, C.D., *et al.* Diagnosing detrusor sphincter dyssynergia in the neurological patient. *BJU Int*, 2012. 109 Suppl 3: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/22458490>
105. Lose, G., *et al.* Standardisation of urethral pressure measurement: report from the Standardisation Sub-Committee of the International Continence Society. *Neurourol Urodyn*, 2002. 21: 258.
<https://www.ncbi.nlm.nih.gov/pubmed/11948719>
106. Marks, B.K., *et al.* Videourodynamics: indications and technique. *Urol Clin North Am*, 2014. 41: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/25063594>
107. Virseda, M., *et al.* Reliability of ambulatory urodynamics in patients with spinal cord injuries. *Neurourology and Urodynamics*, 2013. 32: 387.
<https://www.ncbi.nlm.nih.gov/pubmed/23002043>
108. Virseda-Chamorro, M., *et al.* Comparison of ambulatory versus video urodynamics in patients with spinal cord injury. *Spinal Cord*, 2014. 52: 551.
<https://www.ncbi.nlm.nih.gov/pubmed/24663000>
109. Geirsson, G., *et al.* The ice-water test--a simple and valuable supplement to routine cystometry. *Br J Urol*, 1993. 71: 681.
<https://www.ncbi.nlm.nih.gov/pubmed/8343894>
110. Geirsson, G., *et al.* Pressure, volume and infusion speed criteria for the ice-water test. *Br J Urol*, 1994. 73: 498.
<https://www.ncbi.nlm.nih.gov/pubmed/8012770>
111. Al-Hayek, S., *et al.* The 50-year history of the ice water test in urology. *J Urol*, 2010. 183: 1686.
<https://www.ncbi.nlm.nih.gov/pubmed/20299050>
112. Lapedes, J. Neurogenic bladder. Principles of treatment. *Urol Clin North Am*, 1974. 1: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/4428540>
113. Riedl, C.R., *et al.* Electromotive administration of intravesical bethanechol and the clinical impact on acontractile detrusor management: introduction of a new test. *J Urol*, 2000. 164: 2108.
<https://www.ncbi.nlm.nih.gov/pubmed/11061937>
114. Podnar, S., *et al.* Lower urinary tract dysfunction in patients with peripheral nervous system lesions. *Handb Clin Neurol*, 2015. 130: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/26003246>
115. Ouyang, L., *et al.* Characteristics and survival of patients with end stage renal disease and spina bifida in the United States renal data system. *J Urol*, 2015. 193: 558.
<https://www.ncbi.nlm.nih.gov/pubmed/25167993>
116. Lawrenson, R., *et al.* Renal failure in patients with neurogenic lower urinary tract dysfunction. *Neuroepidemiology*, 2001. 20: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/11359083>
117. Averbek, M.A., *et al.* Follow-up of the neuro-urological patient: a systematic review. *BJU Int*, 2015. 115 Suppl 6: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/>
118. Stöhrer, M., *et al.* Diagnosis and treatment of bladder dysfunction in spinal cord injury patients. *Eur Urol Update Series* 1994. 3: 170. [No abstract available]
119. Drake, M., *et al.*, Conservative management in neuropathic urinary incontinence, in *Incontinence*, P. Abrams, L. Cardozo, S. Khoury & A. Wein, Editors. 2013, Health Publication: Plymouth: , 2013; pp. 827-1000.
120. Chamberlain, J.D., *et al.* Mortality and longevity after a spinal cord injury: systematic review and meta-analysis. *Neuroepidemiology*, 2015. 44: 182.
<https://www.ncbi.nlm.nih.gov/pubmed/25997873>
121. Game, X., *et al.* Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. *Eur Urol*, 2008. 53: 613.
<https://www.ncbi.nlm.nih.gov/pubmed/17804150>
122. Frankel, H.L., *et al.* Long-term survival in spinal cord injury: a fifty year investigation. *Spinal Cord*, 1998. 36: 266.
<https://www.ncbi.nlm.nih.gov/pubmed/9589527>

123. Jamil, F. Towards a catheter free status in neurogenic bladder dysfunction: a review of bladder management options in spinal cord injury (SCI). *Spinal Cord*, 2001. 39: 355.
<https://www.ncbi.nlm.nih.gov/pubmed/11464308>
124. Thietje, R., *et al.* Mortality in patients with traumatic spinal cord injury: descriptive analysis of 62 deceased subjects. *J Spinal Cord Med*, 2011. 34: 482.
<https://www.ncbi.nlm.nih.gov/pubmed/22118255>
125. Hackler, R.H. A 25-year prospective mortality study in the spinal cord injured patient: comparison with the long-term living paraplegic. *J Urol*, 1977. 117: 486.
<https://www.ncbi.nlm.nih.gov/pubmed/850323>
126. Rodrigues, P., *et al.* Involuntary detrusor contraction is a frequent finding in patients with recurrent urinary tract infections. *Urol Int*, 2014. 93: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/>
127. Bauer, S.B. Neurogenic bladder: etiology and assessment. *Pediatr Nephrol*, 2008. 23: 541.
<https://www.ncbi.nlm.nih.gov/pubmed/18270749>
128. Barbalias, G.A., *et al.* Critical evaluation of the Crede maneuver: a urodynamic study of 207 patients. *J Urol*, 1983. 130: 720.
<https://www.ncbi.nlm.nih.gov/pubmed/6887405>
129. Reinberg, Y., *et al.* Renal rupture after the Crede maneuver. *J Pediatr*, 1994. 124: 279.
<https://www.ncbi.nlm.nih.gov/pubmed/8301439>
130. Wyndaele, J.J., *et al.* Neurologic urinary incontinence. *Neurourol Urodyn*, 2010. 29: 159.
<https://www.ncbi.nlm.nih.gov/pubmed/20025021>
131. Menon, E.B., *et al.* Bladder training in patients with spinal cord injury. *Urology*, 1992. 40: 425.
<https://www.ncbi.nlm.nih.gov/pubmed/1441039>
132. Furusawa, K., *et al.* Incidence of symptomatic autonomic dysreflexia varies according to the bowel and bladder management techniques in patients with spinal cord injury. *Spinal Cord*, 2011. 49: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/20697419>
133. Outcomes following traumatic spinal cord injury: clinical practice guidelines for health-care professionals. *J Spinal Cord Med*, 2000. 23: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/17536300>
134. El-Masri, W.S., *et al.* Long-term follow-up study of outcomes of bladder management in spinal cord injury patients under the care of the Midlands Centre for Spinal Injuries in Oswestry. *Spinal Cord*, 2012. 50: 14.
<https://www.ncbi.nlm.nih.gov/pubmed/21808256>
135. Singh, R., *et al.* Bladder management methods and urological complications in spinal cord injury patients. *Indian J Orthop*, 2011. 45: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/21430869>
136. Fall, M., *et al.* Electrical stimulation. A physiologic approach to the treatment of urinary incontinence. *Urol Clin North Am*, 1991. 18: 393.
<https://www.ncbi.nlm.nih.gov/pubmed/2017820>
137. Vodusek, D.B., *et al.* Detrusor inhibition induced by stimulation of pudendal nerve afferents. *Neurourol Urodyn*, 1986. 5: 381.
<http://onlinelibrary.wiley.com/doi/10.1002/nau.1930050404/abstract>
138. Gross, T., *et al.* Transcutaneous Electrical Nerve Stimulation for Treating Neurogenic Lower Urinary Tract Dysfunction: A Systematic Review. *Eur Urol*, 2016. 69: 1102.
[http://www.europeanurology.com/article/S0302-2838\(16\)00061-0/abstract/](http://www.europeanurology.com/article/S0302-2838(16)00061-0/abstract/)
139. Schneider, M.P., *et al.* Tibial Nerve Stimulation for Treating Neurogenic Lower Urinary Tract Dysfunction: A Systematic Review. *Eur Urol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26194043>
140. McClurg, D., *et al.* Neuromuscular electrical stimulation and the treatment of lower urinary tract dysfunction in multiple sclerosis--a double blind, placebo controlled, randomised clinical trial. *Neurourol Urodyn*, 2008. 27: 231.
<https://www.ncbi.nlm.nih.gov/pubmed17705160>
141. McClurg, D., *et al.* Comparison of pelvic floor muscle training, electromyography biofeedback, and neuromuscular electrical stimulation for bladder dysfunction in people with multiple sclerosis: a randomized pilot study. *Neurourol Urodyn*, 2006. 25: 337.
<https://www.ncbi.nlm.nih.gov/pubmed/16637070>
142. Ferreira, A.P., *et al.* Impact of a Pelvic Floor Training Program Among Women with Multiple Sclerosis: A Controlled Clinical Trial. *Am J Phys Med Rehabil*. 2016. 95: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/25888662>

143. Hagerty, J.A., *et al.* Intravesical electrotherapy for neurogenic bladder dysfunction: a 22-year experience. *J Urol*, 2007. 178: 1680.
<https://www.ncbi.nlm.nih.gov/pubmed/17707024>
144. Primus, G., *et al.* Restoration of micturition in patients with acontractile and hypocontractile detrusor by transurethral electrical bladder stimulation. *Neurourol Urodyn*, 1996. 15: 489.
<https://www.ncbi.nlm.nih.gov/pubmed/8857617>
145. Lombardi, G., *et al.* Clinical efficacy of intravesical electrostimulation on incomplete spinal cord patients suffering from chronic neurogenic non-obstructive retention: a 15-year single centre retrospective study. *Spinal Cord*, 2013. 51: 232.
<https://www.ncbi.nlm.nih.gov/pubmed/23147136>
146. Brusa, L., *et al.* Effects of inhibitory rTMS on bladder function in Parkinson's disease patients. *Mov Disord*, 2009. 24: 445.
<https://www.ncbi.nlm.nih.gov/pubmed/19133657>
147. Centonze, D., *et al.* Effects of motor cortex rTMS on lower urinary tract dysfunction in multiple sclerosis. *Mult Scler*, 2007. 13: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/17439897>
148. Thomas, L.H., *et al.* Treatment of urinary incontinence after stroke in adults. *Cochrane Database Syst Rev*, 2008: Cd004462.
<https://www.ncbi.nlm.nih.gov/pubmed/18254050>
149. Yeo, L., *et al.* Urinary tract dysfunction in Parkinson's disease: a review. *Int Urol Nephrol*, 2012. 44: 415.
<https://www.ncbi.nlm.nih.gov/pubmed/21553114>
150. Phe, V., *et al.* Management of neurogenic bladder in patients with multiple sclerosis. *Nat Rev Urol*, 2016. 13: 275.
<https://www.ncbi.nlm.nih.gov/pubmed/27030526>
151. Stohrer, M., *et al.* EAU guidelines on neurogenic lower urinary tract dysfunction. *Eur Urol*, 2009. 56: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/19403235>
152. Andersson, K.E. Antimuscarinic mechanisms and the overactive detrusor: an update. *Eur Urol*, 2011. 59: 377.
<https://www.ncbi.nlm.nih.gov/pubmed/21168951>
153. Kennelly, M.J., *et al.* Overactive bladder: pharmacologic treatments in the neurogenic population. *Rev Urol*, 2008. 10: 182.
<https://www.ncbi.nlm.nih.gov/pubmed/18836537>
154. Madersbacher, H., *et al.* Neurogenic detrusor overactivity in adults: a review on efficacy, tolerability and safety of oral antimuscarinics. *Spinal Cord*, 2013. 51: 432.
<https://www.ncbi.nlm.nih.gov/pubmed/23743498>
155. Madhuvrata, P., *et al.* Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis. *Eur Urol*, 2012. 62: 816.
<https://www.ncbi.nlm.nih.gov/pubmed/22397851>
156. Bennett, N., *et al.* Can higher doses of oxybutynin improve efficacy in neurogenic bladder? *J Urol*, 2004. 171: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/14713802>
157. Horstmann, M., *et al.* Neurogenic bladder treatment by doubling the recommended antimuscarinic dosage. *Neurourol Urodyn*, 2006. 25: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/16847942>
158. Mehnert, U., *et al.* The management of urinary incontinence in the male neurological patient. *Curr Opin Urol*, 2014. 24: 586.
<https://www.ncbi.nlm.nih.gov/pubmed/25389549>
159. Stothers, L., *et al.* An integrative review of standardized clinical evaluation tool utilization in anticholinergic drug trials for neurogenic lower urinary tract dysfunction. *Spinal Cord*, 2016. 31: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/27241452>
160. Amend, B., *et al.* Effective treatment of neurogenic detrusor dysfunction by combined high-dosed antimuscarinics without increased side-effects. *Eur Urol*, 2008. 53: 1021.
<https://www.ncbi.nlm.nih.gov/pubmed/18243516>
161. Cameron, A.P. Pharmacologic therapy for the neurogenic bladder. *Urol Clin North Am*, 2010. 37: 495.
<https://www.ncbi.nlm.nih.gov/pubmed/20955901>

162. Menarini, M., *et al.* Trosipium chloride in patients with neurogenic detrusor overactivity: is dose titration of benefit to the patients? *Int J Clin Pharmacol Ther*, 2006. 44: 623.
<https://www.ncbi.nlm.nih.gov/pubmed/17190372>
163. Nardulli, R., *et al.* Combined antimuscarinics for treatment of neurogenic overactive bladder. *Int J Immunopathol Pharmacol*, 2012. 25: 35s.
<https://www.ncbi.nlm.nih.gov/pubmed/22652160>
164. Cameron, A.P., *et al.* Combination drug therapy improves compliance of the neurogenic bladder. *J Urol*, 2009. 182: 1062.
<https://www.ncbi.nlm.nih.gov/pubmed/19616807>
165. Isik, A.T., *et al.* Trosipium and cognition in patients with late onset Alzheimer disease. *J Nutr Health Aging*, 2009. 13: 672.
<https://www.ncbi.nlm.nih.gov/pubmed/19657549>
166. Ethans, K.D., *et al.* Efficacy and safety of tolterodine in people with neurogenic detrusor overactivity. *J Spinal Cord Med*, 2004. 27: 214.
<https://www.ncbi.nlm.nih.gov/pubmed/15478523>
167. McKeage, K. Propiverine: A review of its use in the treatment of adults and children with overactive bladder associated with idiopathic or neurogenic detrusor overactivity, and in men with lower urinary tract symptoms. *Clin Drug Investig*, 2013. 33: 71.
<https://www.ncbi.nlm.nih.gov/pubmed/23288694>
168. Nicholas, R.S., *et al.* Anticholinergics for urinary symptoms in multiple sclerosis. *Cochrane Database Syst Rev*, 2009: Cd004193.
<https://www.ncbi.nlm.nih.gov/pubmed/19160231>
169. van Rey, F., *et al.* Solifenacin in multiple sclerosis patients with overactive bladder: a prospective study. *Adv Urol*, 2011. 2011: 834753.
<https://www.ncbi.nlm.nih.gov/pubmed/21687581>
170. Bycroft, J., *et al.* The effect of darifenacin on neurogenic detrusor overactivity in patients with spinal cord injury. *Neurourol Urodyn* 2003. 22: A190.
<https://www.ics.org/Abstracts/Publish/41/000190.pdf>
171. Carl, S., *et al.* Darifenacin is also effective in neurogenic bladder dysfunction (multiple sclerosis). *Urology*, 2006. 68 250. [No abstract available]
172. Krebs, J., *et al.* Effects of solifenacin in patients with neurogenic detrusor overactivity as a result of spinal cord lesion. *Spinal Cord*, 2013. 51: 306.
<https://www.ncbi.nlm.nih.gov/pubmed/23247012>
173. Amarenco, G., *et al.* Solifenacin is effective and well tolerated in patients with neurogenic detrusor overactivity: Results from the double-blind, randomized, active- and placebo-controlled SONIC urodynamic study. *Neurourol Urodyn*, 2015. 29: 29.
<https://www.ncbi.nlm.nih.gov/pubmed/26714009>
174. Zesiewicz, T.A., *et al.* Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease. *Parkinsonism Relat Disord*, 2015. 21: 514.
<https://www.ncbi.nlm.nih.gov/pubmed/25814050>
175. Sakakibara, R., *et al.* Imidafenacin on bladder and cognitive function in neurologic OAB patients. *Clin Auton Res*, 2013. 23: 189.
<https://www.ncbi.nlm.nih.gov/pubmed/23820664>
176. Stohrer, M., *et al.* Efficacy and tolerability of propiverine hydrochloride extended-release compared with immediate-release in patients with neurogenic detrusor overactivity. *Spinal Cord*, 2013. 51: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/23338657>
177. Caremel, R., *et al.* [Drug therapy of bladder dysfunction]. *Prog Urol*. 2013 Nov;23(15):1271-86.
<https://www.ncbi.nlm.nih.gov/pubmed/24183086>
178. Wollner, J., *et al.* Initial experience with the treatment of neurogenic detrusor overactivity with a new beta-3 agonist (mirabegron) in patients with spinal cord injury. *Spinal Cord*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26503222>
179. Welk, B. Urodynamic and Clinical Efficacy of Mirabegron for Neurogenic Bladder Patients, Ongoing study: *Clinical Trials*. Gov Identifier NCT02044510.
<https://clinicaltrials.gov/ct2/show/NCT02044510>
180. Abrams, P., *et al.* Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (Symphony). *Eur Urol*, 2015. 67: 577.
<https://www.ncbi.nlm.nih.gov/pubmed/24612659>

181. Barendrecht, M.M., *et al.* Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based? *BJU Int*, 2007. 99: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/17233798>
182. Apostolidis, A. Taming the cannabinoids: new potential in the pharmacologic control of lower urinary tract dysfunction. *Eur Urol*, 2012. 61: 107.
<https://www.ncbi.nlm.nih.gov/pubmed/21996529>
183. Gratzke, C., *et al.* Effects of cannabimimetic, a novel selective cannabinoid 2 receptor agonist, on bladder function in normal rats. *Eur Urol*, 2010. 57: 1093.
<https://www.ncbi.nlm.nih.gov/pubmed/20207474>
184. Koppel, B.S., *et al.* Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*, 2014. 82: 1556.
<https://www.ncbi.nlm.nih.gov/pubmed/24778283>
185. Abrams, P., *et al.* Tamsulosin: efficacy and safety in patients with neurogenic lower urinary tract dysfunction due to suprasacral spinal cord injury. *J Urol*, 2003. 170: 1242.
<https://www.ncbi.nlm.nih.gov/pubmed/14501734>
186. Gomes, C.M., *et al.* Neurological status predicts response to alpha-blockers in men with voiding dysfunction and Parkinson's disease. *Clinics*, 2014. 69: 817.
<https://www.ncbi.nlm.nih.gov/pubmed/25627993>
187. Moon, K.H., *et al.* A 12-week, open label, multi-center study to evaluate the clinical efficacy and safety of silodosin on voiding dysfunction in patients with neurogenic bladder. *Low Urin Tract Symptoms*, 2015. 7: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/26663648>
188. Guttmann, L., *et al.* The value of intermittent catheterisation in the early management of traumatic paraplegia and tetraplegia. *Paraplegia*, 1966. 4: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/5969402>
189. Lapidis, J., *et al.* Clean, intermittent self-catheterization in the treatment of urinary tract disease. *J Urol*, 1972. 107: 458.
<https://www.ncbi.nlm.nih.gov/pubmed/5010715>
190. Wyndaele, J.J. Intermittent catheterization: which is the optimal technique? *Spinal Cord*, 2002. 40: 432.
<https://www.ncbi.nlm.nih.gov/pubmed/12185603>
191. Prieto-Fingerhut, T., *et al.* A study comparing sterile and nonsterile urethral catheterization in patients with spinal cord injury. *Rehabil Nurs*, 1997. 22: 299.
<https://www.ncbi.nlm.nih.gov/pubmed/9416190>
192. Kiddoo, D., *et al.* Randomized Crossover Trial of Single Use Hydrophilic Coated vs Multiple Use Polyvinylchloride Catheters for Intermittent Catheterization to Determine Incidence of Urinary Infection. *J Urol*, 2015. 194: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/25584995>
193. Günther, M., *et al.* Auswirkungen des aseptischen intermittierenden Katheterismus auf die männliche Harnröhre. *Der Urologe B*, 2001. 41: 359.
<http://link.springer.com/article/10.1007/s001310170044>
194. Bakke, A., *et al.* Physical predictors of infection in patients treated with clean intermittent catheterization: a prospective 7-year study. *Br J Urol*, 1997. 79: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/9043503>
195. Waller, L., *et al.* Clean intermittent catheterization in spinal cord injury patients: long-term followup of a hydrophilic low friction technique. *J Urol*, 1995. 153: 345.
<https://www.ncbi.nlm.nih.gov/pubmed/7815579>
196. Wyndaele, J.J. Complications of intermittent catheterization: their prevention and treatment. *Spinal Cord*, 2002. 40: 536.
<https://www.ncbi.nlm.nih.gov/pubmed/12235537>
197. Kurze, I., *et al.* Intermittent Catheterisation and Prevention of Urinary Tract Infections in Patients with Neurogenic Lower Urinary Tract Dysfunction - Best PracticeAn Overview. [German]. *Aktuelle Neurologie*, 2015. 42: 515. [No abstract available]
198. Woodbury, M.G., *et al.* Intermittent catheterization practices following spinal cord injury: a national survey. *Can J Urol*, 2008. 15: 4065.
<https://www.ncbi.nlm.nih.gov/pubmed/18570710>
199. Weld, K.J., *et al.* Effect of bladder management on urological complications in spinal cord injured patients. *J Urol*, 2000. 163: 768.
<https://www.ncbi.nlm.nih.gov/pubmed/10687973>

200. Bennett, C.J., *et al.* Comparison of bladder management complication outcomes in female spinal cord injury patients. *J Urol*, 1995. 153: 1458.
<https://www.ncbi.nlm.nih.gov/pubmed/7714965>
201. Chancellor, M.B., *et al.* Functional urethral closure with pubovaginal sling for destroyed female urethra after long-term urethral catheterization. *Urology*, 1994. 43: 499.
<https://www.ncbi.nlm.nih.gov/pubmed/8154071>
202. Chao, R., *et al.* Fate of upper urinary tracts in patients with indwelling catheters after spinal cord injury. *Urology*, 1993. 42: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/>
203. Larsen, L.D., *et al.* Retrospective analysis of urologic complications in male patients with spinal cord injury managed with and without indwelling urinary catheters. *Urology*, 1997. 50: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/9301708>
204. Mitsui, T., *et al.* Is suprapubic cystostomy an optimal urinary management in high quadriplegics?. A comparative study of suprapubic cystostomy and clean intermittent catheterization. *Eur Urol*, 2000. 38: 434.
<https://www.ncbi.nlm.nih.gov/pubmed/11025382>
205. Park, Y.I., *et al.* A method to minimize indwelling catheter calcification and bladder stones in individuals with spinal cord injury. *J Spinal Cord Med*, 2001. 24: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/11587416>
206. Weld, K.J., *et al.* Influences on renal function in chronic spinal cord injured patients. *J Urol*, 2000. 164: 1490.
<https://www.ncbi.nlm.nih.gov/pubmed/11025689>
207. West, D.A., *et al.* Role of chronic catheterization in the development of bladder cancer in patients with spinal cord injury. *Urology*, 1999. 53: 292.
<https://www.ncbi.nlm.nih.gov/pubmed/9933042>
208. Hollingsworth, J.M., *et al.* Determining the noninfectious complications of indwelling urethral catheters: a systematic review and meta-analysis. *Ann Intern Med*, 2013. 159: 401.
<https://www.ncbi.nlm.nih.gov/pubmed/24042368>
209. Di Stasi, S.M., *et al.* Intravesical oxybutynin: mode of action assessed by passive diffusion and electromotive administration with pharmacokinetics of oxybutynin and N-desethyl oxybutynin. *J Urol*, 2001. 166: 2232.
<https://www.ncbi.nlm.nih.gov/pubmed/11696741>
210. Buyse, G., *et al.* Intravesical oxybutynin for neurogenic bladder dysfunction: less systemic side effects due to reduced first pass metabolism. *J Urol*, 1998. 160: 892.
<https://www.ncbi.nlm.nih.gov/pubmed/9720583>
211. Haferkamp, A., *et al.* Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. *Spinal Cord*, 2000. 38: 250.
<https://www.ncbi.nlm.nih.gov/pubmed/10822396>
212. Pannek, J., *et al.* Combined intravesical and oral oxybutynin chloride in adult patients with spinal cord injury. *Urology*, 2000. 55: 358.
<https://www.ncbi.nlm.nih.gov/pubmed/10699610>
213. Schroder, A., *et al.* Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomized, prospective, controlled multi-center trial. *Neurourol Urodyn*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25754454>
214. Geirsson, G., *et al.* Clinical and urodynamic effects of intravesical capsaicin treatment in patients with chronic traumatic spinal detrusor hyperreflexia. *J Urol*, 1995. 154: 1825.
<https://www.ncbi.nlm.nih.gov/pubmed/7563356>
215. Giannantoni, A., *et al.* Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. *J Urol*, 2004. 172: 240.
<https://www.ncbi.nlm.nih.gov/pubmed/15201783>
216. Kim, J.H., *et al.* Intravesical resiniferatoxin for refractory detrusor hyperreflexia: a multicenter, blinded, randomized, placebo-controlled trial. *J Spinal Cord Med*, 2003. 26: 358.
<https://www.ncbi.nlm.nih.gov/pubmed/14992337>
217. Del Popolo, G., *et al.* Neurogenic detrusor overactivity treated with english botulinum toxin a: 8-year experience of one single centre. *Eur Urol*, 2008. 53: 1013.
<https://www.ncbi.nlm.nih.gov/pubmed/17950989>

218. Reitz, A., *et al.* European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. *Eur Urol*, 2004. 45: 510.
<https://www.ncbi.nlm.nih.gov/pubmed/15041117>
219. Schurch, B., *et al.* Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. *J Urol*, 2005. 174: 196.
<https://www.ncbi.nlm.nih.gov/pubmed/15947626>
220. Cruz, F., *et al.* Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. *Eur Urol*, 2011. 60: 742.
<https://www.ncbi.nlm.nih.gov/pubmed/21798658>
221. Mehta, S., *et al.* Meta-analysis of botulinum toxin A detrusor injections in the treatment of neurogenic detrusor overactivity after spinal cord injury. *Arch Phys Med Rehabil*, 2013. 94: 1473.
<https://www.ncbi.nlm.nih.gov/pubmed/23632286>
222. Mangera, A., *et al.* An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. *Eur Urol*, 2014. 65: 981.
<https://www.ncbi.nlm.nih.gov/pubmed/24239446>
223. Ginsberg, D., *et al.* Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. *J Urol*, 2012. 187: 2131.
<https://www.ncbi.nlm.nih.gov/pubmed/22503020>
224. Grosse, J., *et al.* Success of repeat detrusor injections of botulinum a toxin in patients with severe neurogenic detrusor overactivity and incontinence. *Eur Urol*, 2005. 47: 653.
<https://www.ncbi.nlm.nih.gov/pubmed/15826758>
225. Dykstra, D.D., *et al.* Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double-blind study. *Arch Phys Med Rehabil*, 1990. 71: 24.
<https://www.ncbi.nlm.nih.gov/pubmed/2297305>
226. Petit, H., *et al.* Botulinum A toxin treatment for detrusor-sphincter dyssynergia in spinal cord disease. *Spinal Cord*, 1998. 36: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/9494997>
227. Schurch, B., *et al.* Botulinum-A toxin as a treatment of detrusor-sphincter dyssynergia: a prospective study in 24 spinal cord injury patients. *J Urol*, 1996. 155: 1023.
<https://www.ncbi.nlm.nih.gov/pubmed/8583552>
228. Utomo, E., *et al.* Surgical management of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction. *Cochrane Database Syst Rev*, 2014. 5: Cd004927.
<https://www.ncbi.nlm.nih.gov/pubmed/24859260>
229. Chancellor, M.B., *et al.* Prospective comparison of external sphincter balloon dilatation and prosthesis placement with external sphincterotomy in spinal cord injured men. *Arch Phys Med Rehabil*, 1994. 75: 297.
<https://www.ncbi.nlm.nih.gov/pubmed/8129583>
230. Perikash, I. Use of contact laser crystal tip firing Nd:YAG to relieve urinary outflow obstruction in male neurogenic bladder patients. *J Clin Laser Med Surg*, 1998. 16: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/9728128>
231. Reynard, J.M., *et al.* Sphincterotomy and the treatment of detrusor-sphincter dyssynergia: current status, future prospects. *Spinal Cord*, 2003. 41: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/12494314>
232. Noll, F., *et al.* Transurethral sphincterotomy in quadriplegic patients: long-term-follow-up. *Neurourol Urodyn*, 1995. 14: 351.
<https://www.ncbi.nlm.nih.gov/pubmed/7581471>
233. Derry, F., *et al.* Audit of bladder neck resection in spinal cord injured patients. *Spinal Cord*, 1998. 36: 345.
<https://www.ncbi.nlm.nih.gov/pubmed/9601115>
234. Chancellor, M.B., *et al.* Long-term followup of the North American multicenter UroLume trial for the treatment of external detrusor-sphincter dyssynergia. *J Urol*, 1999. 161: 1545.
<https://www.ncbi.nlm.nih.gov/pubmed/10210393>
235. Seoane-Rodriguez, S., *et al.* Long-term follow-up study of intraurethral stents in spinal cord injured patients with detrusor-sphincter dyssynergia. *Spinal Cord*, 2007. 45: 621.
<https://www.ncbi.nlm.nih.gov/pubmed/17211463>

236. Gajewski, J.B., *et al.* Removal of UroLume endoprosthesis: experience of the North American Study Group for detrusor-sphincter dyssynergia application. *J Urol*, 2000. 163: 773.
<https://www.ncbi.nlm.nih.gov/pubmed/10687974>
237. Wilson, T.S., *et al.* UroLume stents: lessons learned. *J Urol*, 2002. 167: 2477.
<https://www.ncbi.nlm.nih.gov/pubmed/11992061>
238. Polguer, T., *et al.* [Treatment of detrusor-striated sphincter dyssynergia with permanent nitinol urethral stent: results after a minimum follow-up of 2 years]. *Prog Urol*, 2012. 22: 1058.
<https://www.ncbi.nlm.nih.gov/pubmed/23182120>
239. van der Merwe, A., *et al.* Outcome of dual flange metallic urethral stents in the treatment of neuropathic bladder dysfunction after spinal cord injury. *J Endourol*, 2012. 26: 1210.
<https://www.ncbi.nlm.nih.gov/pubmed/22519741>
240. Pannek, J., *et al.* Clinical usefulness of the memokath stent as a second-line procedure after sphincterotomy failure. *J Endourol*, 2011. 25: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/20977372>
241. Abdul-Rahman, A., *et al.* A 20-year follow-up of the mesh wallstent in the treatment of detrusor external sphincter dyssynergia in patients with spinal cord injury. *BJU Int*, 2010. 106: 1510.
<https://www.ncbi.nlm.nih.gov/pubmed/20500511>
242. Bennett, J.K., *et al.* Collagen injections for intrinsic sphincter deficiency in the neuropathic urethra. *Paraplegia*, 1995. 33: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/8927407>
243. Block, C.A., *et al.* Long-term efficacy of periurethral collagen injection for the treatment of urinary incontinence secondary to myelomeningocele. *J Urol*, 2003. 169: 327.
<https://www.ncbi.nlm.nih.gov/pubmed/12478183>
244. Schurch, B., *et al.* Intraurethral sphincter prosthesis to treat hyporeflexic bladders in women: does it work? *BJU Int*, 1999. 84: 789.
<https://www.ncbi.nlm.nih.gov/pubmed/10532973>
245. Barthold, J.S., *et al.* Results of the rectus fascial sling and wrap procedures for the treatment of neurogenic sphincteric incontinence. *J Urol*, 1999. 161: 272.
<https://www.ncbi.nlm.nih.gov/pubmed/10037423>
246. Daneshmand, S., *et al.* Puboprosthetic sling repair for treatment of urethral incompetence in adult neurogenic incontinence. *J Urol*, 2003. 169: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/12478135>
247. Gormley, E.A., *et al.* Pubovaginal slings for the management of urinary incontinence in female adolescents. *J Urol*, 1994. 152: 822.
<https://www.ncbi.nlm.nih.gov/pubmed/8022024>
248. Herschorn, S., *et al.* Fascial slings and bladder neck tapering in the treatment of male neurogenic incontinence. *J Urol*, 1992. 147: 1073.
<https://www.ncbi.nlm.nih.gov/pubmed/1552586>
249. Kakizaki, H., *et al.* Fascial sling for the management of urinary incontinence due to sphincter incompetence. *J Urol*, 1995. 153: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/7861504>
250. Mingin, G.C., *et al.* The rectus myofascial wrap in the management of urethral sphincter incompetence. *BJU Int*, 2002. 90: 550.
<https://www.ncbi.nlm.nih.gov/pubmed/12230615>
251. Abdul-Rahman, A., *et al.* Long-term outcome of tension-free vaginal tape for treating stress incontinence in women with neuropathic bladders. *BJU Int*, 2010. 106: 827.
<https://www.ncbi.nlm.nih.gov/pubmed/20132201>
252. Losco, G.S., *et al.* Long-term outcome of transobturator tape (TOT) for treatment of stress urinary incontinence in females with neuropathic bladders. *Spinal Cord*, 2015. 53: 544.
<https://www.ncbi.nlm.nih.gov/pubmed/25917951>
253. El-Azab, A.S., *et al.* Midurethral slings versus the standard pubovaginal slings for women with neurogenic stress urinary incontinence. *Int Urogynecol J*, 2015. 26: 427.
<https://www.ncbi.nlm.nih.gov/pubmed/25315169>
254. Athanasopoulos, A., *et al.* Treating stress urinary incontinence in female patients with neuropathic bladder: the value of the autologous fascia rectus sling. *Int Urol Nephrol*, 2012. 44: 1363.
<https://www.ncbi.nlm.nih.gov/pubmed/22821050>
255. Groen, L.A., *et al.* The AdVance male sling as a minimally invasive treatment for intrinsic sphincter deficiency in patients with neurogenic bladder sphincter dysfunction: a pilot study. *Neurourology and Urodynamics*, 2012. 31: 1284.
<https://www.ncbi.nlm.nih.gov/pubmed/22847896>

256. Mehnert, U., *et al.* Treatment of neurogenic stress urinary incontinence using an adjustable continence device: 4-year followup. *J Urol*, 2012. 188: 2274.
<https://www.ncbi.nlm.nih.gov/pubmed/23083648>
257. Light, J.K., *et al.* Use of the artificial urinary sphincter in spinal cord injury patients. *J Urol*, 1983. 130: 1127.
<https://www.ncbi.nlm.nih.gov/pubmed/6644893>
258. Costa, P., *et al.* Long-term results of artificial urinary sphincter for women with type III stress urinary incontinence. *Eur Urol*, 2013. 63: 753.
<https://www.ncbi.nlm.nih.gov/pubmed/22445222>
259. Thomas, K., *et al.* Outcome of the artificial urinary sphincter in female patients. *J Urol*, 2002. 167: 1720.
<https://www.ncbi.nlm.nih.gov/pubmed/11912395>
260. Chartier Kastler, E., *et al.* Treatment of neurogenic male urinary incontinence related to intrinsic sphincter insufficiency with an artificial urinary sphincter: a French retrospective multicentre study. *BJU Int*, 2011. 107: 426.
<https://www.ncbi.nlm.nih.gov/pubmed/20633005>
261. Elliott, D.S., *et al.* Mayo Clinic long-term analysis of the functional durability of the AMS 800 artificial urinary sphincter: a review of 323 cases. *J Urol*, 1998. 159: 1206.
<https://www.ncbi.nlm.nih.gov/pubmed/9507835>
262. Fulford, S.C., *et al.* The fate of the 'modern' artificial urinary sphincter with a follow-up of more than 10 years. *Br J Urol*, 1997. 79: 713.
<https://www.ncbi.nlm.nih.gov/pubmed/9158507>
263. Viers, B.R., *et al.* Simultaneous augmentation cystoplasty and cuff only artificial urinary sphincter in children and young adults with neurogenic urinary incontinence. *J Urol*, 2014. 191: 1104.
<https://www.ncbi.nlm.nih.gov/pubmed/24060640>
264. Janknegt, R.A., *et al.* Electrically stimulated gracilis sphincter for treatment of bladder sphincter incontinence. *Lancet*, 1992. 340: 1129.
<https://www.ncbi.nlm.nih.gov/pubmed/1359213>
265. Chancellor, M.B., *et al.* Gracilis muscle transposition with electrical stimulation for sphincteric incontinence: a new approach. *World J Urol*, 1997. 15: 320.
<https://www.ncbi.nlm.nih.gov/pubmed/9372585>
266. Chancellor, M.B., *et al.* Gracilis urethromyoplasty--an autologous urinary sphincter for neurologically impaired patients with stress incontinence. *Spinal Cord*, 1997. 35: 546.
<https://www.ncbi.nlm.nih.gov/pubmed/9267922>
267. Donnahoo, K.K., *et al.* The Young-Dees-Leadbetter bladder neck repair for neurogenic incontinence. *J Urol*, 1999. 161: 1946.
<https://www.ncbi.nlm.nih.gov/pubmed/10332478>
268. Kropp, K.A., *et al.* Urethral lengthening and reimplantation for neurogenic incontinence in children. *J Urol*, 1986. 135: 533.
<https://www.ncbi.nlm.nih.gov/pubmed/3944902>
269. Salle, J.L., *et al.* Urethral lengthening with anterior bladder wall flap (Pippi Salle procedure): modifications and extended indications of the technique. *J Urol*, 1997. 158: 585.
<https://www.ncbi.nlm.nih.gov/pubmed/9224369>
270. Rawashdeh, Y.F., *et al.* International Children's Continence Society's recommendations for therapeutic intervention in congenital neuropathic bladder and bowel dysfunction in children. *Neurourol Urodyn*, 2012. 31: 615.
<https://www.ncbi.nlm.nih.gov/pubmed/22532368>
271. Nagib, A., *et al.* Successful control of selective anterior sacral rhizotomy for treatment of spastic bladder and ureteric reflux in paraplegics. *Med Serv J Can*, 1966. 22: 576.
<https://www.ncbi.nlm.nih.gov/pubmed/5966992>
272. Schneidau, T., *et al.* Selective sacral rhizotomy for the management of neurogenic bladders in spina bifida patients: long-term followup. *J Urol*, 1995. 154: 766.
<https://www.ncbi.nlm.nih.gov/pubmed/7609174>
273. Young, B., *et al.* Percutaneous sacral rhizotomy for neurogenic detrusor hyperreflexia. *J Neurosurg*, 1980. 53: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/7411212>
274. Koldewijn, E.L., *et al.* Bladder compliance after posterior sacral root rhizotomies and anterior sacral root stimulation. *J Urol*, 1994. 151: 955.
<https://www.ncbi.nlm.nih.gov/pubmed/8126835>

275. Krasmik, D., *et al.* Urodynamic results, clinical efficacy, and complication rates of sacral intradural deafferentation and sacral anterior root stimulation in patients with neurogenic lower urinary tract dysfunction resulting from complete spinal cord injury. *Neurourol Urodyn*, 2014. 33: 1202.
<https://www.ncbi.nlm.nih.gov/pubmed/24038405>
276. Singh, G., *et al.* Intravesical oxybutynin in patients with posterior rhizotomies and sacral anterior root stimulators. *Neurourol Urodyn*, 1995. 14: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/7742851>
277. Van Kerrebroeck, P.E., *et al.* Results of the treatment of neurogenic bladder dysfunction in spinal cord injury by sacral posterior root rhizotomy and anterior sacral root stimulation. *J Urol*, 1996. 155: 1378.
<https://www.ncbi.nlm.nih.gov/pubmed/8632580>
278. Kutzenberger, J.S. Surgical therapy of neurogenic detrusor overactivity (hyperreflexia) in paraplegic patients by sacral deafferentation and implant driven micturition by sacral anterior root stimulation: methods, indications, results, complications, and future prospects. *Acta Neurochir Suppl*, 2007. 97: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/17691394>
279. Bhadra, N., *et al.* Selective suppression of sphincter activation during sacral anterior nerve root stimulation. *Neurourol Urodyn*, 2002. 21: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/11835425>
280. Kirkham, A.P., *et al.* Neuromodulation through sacral nerve roots 2 to 4 with a Finetech-Brindley sacral posterior and anterior root stimulator. *Spinal Cord*, 2002. 40: 272.
<https://www.ncbi.nlm.nih.gov/pubmed/12037708>
281. Schumacher, S., *et al.* Extradural cold block for selective neurostimulation of the bladder: development of a new technique. *J Urol*, 1999. 161: 950.
<https://www.ncbi.nlm.nih.gov/pubmed/10022732>
282. Brindley, G.S. An implant to empty the bladder or close the urethra. *J Neurol Neurosurg Psychiatry*, 1977. 40: 358.
<https://www.ncbi.nlm.nih.gov/pubmed/406364>
283. Benard, A., *et al.* Comparative cost-effectiveness analysis of sacral anterior root stimulation for rehabilitation of bladder dysfunction in spinal cord injured patients. *Neurosurgery*, 2013. 73: 600.
<https://www.ncbi.nlm.nih.gov/pubmed/23787880>
284. Martens, F.M., *et al.* Quality of life in complete spinal cord injury patients with a Brindley bladder stimulator compared to a matched control group. *Neurourol Urodyn*, 2011. 30: 551.
<https://www.ncbi.nlm.nih.gov/pubmed/21328472>
285. Krebs, J., *et al.* Charcot arthropathy of the spine in spinal cord injured individuals with sacral deafferentation and anterior root stimulator implantation. *Neurourol Urodyn*, 2016. 35: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/25524388>
286. Wollner, J., *et al.* Surgery Illustrated - surgical atlas sacral neuromodulation. *BJU Int*, 2012. 110: 146.
<https://www.ncbi.nlm.nih.gov/pubmed/22691023>
287. Kessler, T.M., *et al.* Sacral neuromodulation for neurogenic lower urinary tract dysfunction: systematic review and meta-analysis. *Eur Urol*, 2010. 58: 865.
<https://www.ncbi.nlm.nih.gov/pubmed/20934242>
288. Lombardi, G., *et al.* Sacral neuromodulation for neurogenic non-obstructive urinary retention in incomplete spinal cord patients: a ten-year follow-up single-centre experience. *Spinal Cord*, 2014. 52: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/24394604>
289. Lay, A.H., *et al.* The role of neuromodulation in patients with neurogenic overactive bladder. *Curr Urol Rep*, 2012. 13: 343.
<https://www.ncbi.nlm.nih.gov/pubmed/22865208>
290. Puccini, F., *et al.* Sacral neuromodulation: an effective treatment for lower urinary tract symptoms in multiple sclerosis. *Int Urogynecol J*. 2016. 27: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/26156206>
291. Zhang, Y.H., *et al.* Enveloping the bladder with displacement of flap of the rectus abdominis muscle for the treatment of neurogenic bladder. *J Urol*, 1990. 144: 1194.
<https://www.ncbi.nlm.nih.gov/pubmed/2146404>
292. Stenzl, A., *et al.* Restoration of voluntary emptying of the bladder by transplantation of innervated free skeletal muscle. *Lancet*, 1998. 351: 1483.
<https://www.ncbi.nlm.nih.gov/pubmed/9605805>

293. Gakis, G., *et al.* Functional detrusor myoplasty for bladder acontractility: long-term results. *J Urol*, 2011. 185: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/21168866>
294. Ninkovic, M., *et al.* The latissimus dorsi detrusor myoplasty for functional treatment of bladder acontractility. *Clin Plast Surg*, 2012. 39: 507.
<https://www.ncbi.nlm.nih.gov/pubmed/23036300>
295. Braren, V., *et al.* Laparoscopic bladder autoaugmentation in children. *Urol Clin North Am*, 1998. 25: 533.
<https://www.ncbi.nlm.nih.gov/pubmed/9728222>
296. Cartwright, P.C., *et al.* Bladder autoaugmentation: early clinical experience. *J Urol*, 1989. 142: 505.
<https://www.ncbi.nlm.nih.gov/pubmed/2746767>
297. Duel, B.P., *et al.* Alternative techniques for augmentation cystoplasty. *J Urol*, 1998. 159: 998.
<https://www.ncbi.nlm.nih.gov/pubmed/9474216>
298. Poppas, D.P., *et al.* Laparoscopic laser assisted auto-augmentation of the pediatric neurogenic bladder: early experience with urodynamic followup. *J Urol*, 1996. 155: 1057.
<https://www.ncbi.nlm.nih.gov/pubmed/8583564>
299. Snow, B.W., *et al.* Bladder autoaugmentation. *Urol Clin North Am*, 1996. 23: 323.
<https://www.ncbi.nlm.nih.gov/pubmed/8659030>
300. Stohrer, M., *et al.* Bladder autoaugmentation--an alternative for enterocystoplasty: preliminary results. *Neurourol Urodyn*, 1995. 14: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/7742844>
301. Stohrer, M., *et al.* Bladder autoaugmentation in adult patients with neurogenic voiding dysfunction. *Spinal Cord*, 1997. 35: 456.
<https://www.ncbi.nlm.nih.gov/pubmed/9232751>
302. Vainrib, M., *et al.* Differences in urodynamic study variables in adult patients with neurogenic bladder and myelomeningocele before and after augmentation enterocystoplasty. *Neurourol Urodyn*, 2013. 32: 250.
<https://www.ncbi.nlm.nih.gov/pubmed/22965686>
303. Krebs, J., *et al.* Functional outcome of supratrigonal cystectomy and augmentation ileocystoplasty in adult patients with refractory neurogenic lower urinary tract dysfunction. *Neurourol Urodyn*, 2014.
<https://www.ncbi.nlm.nih.gov/pubmed/25524480>
304. Gough, D.C. Enterocystoplasty. *BJU Int*, 2001. 88: 739.
<https://www.ncbi.nlm.nih.gov/pubmed/11890246>
305. Greenwell, T.J., *et al.* Augmentation cystoplasty. *BJU Int*, 2001. 88: 511.
<https://www.ncbi.nlm.nih.gov/pubmed/11678743>
306. Vajda, P., *et al.* Histological findings after colcystoplasty and gastrocystoplasty. *J Urol*, 2002. 168: 698.
<https://www.ncbi.nlm.nih.gov/pubmed/12131353>
307. Mitsui, T., *et al.* Preoperative renal scar as a risk factor of postoperative metabolic acidosis following ileocystoplasty in patients with neurogenic bladder. *Spinal Cord*, 2014. 52: 292.
<https://www.ncbi.nlm.nih.gov/pubmed/24469144>
308. Chapple, C.R., *et al.* Surgery for detrusor overactivity. *World J Urol*, 1998. 16: 268.
<https://www.ncbi.nlm.nih.gov/pubmed/9775426>
309. Comer, M.T., *et al.* Reconstruction of the urinary bladder by auto-augmentation, enterocystoplasty, and composite enterocystoplasty. *Adv Exp Med Biol*, 1999. 462: 43.
<https://www.ncbi.nlm.nih.gov/pubmed/10599412>
310. Cranidis, A., *et al.* Bladder augmentation. *Int Urogynecol J Pelvic Floor Dysfunct*, 2000. 11: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/10738932>
311. Leng, W.W., *et al.* Enterocystoplasty or detrusor myectomy? Comparison of indications and outcomes for bladder augmentation. *J Urol*, 1999. 161: 758.
<https://www.ncbi.nlm.nih.gov/pubmed/10022679>
312. Niknejad, K.G., *et al.* Bladder augmentation techniques in women. *Int Urogynecol J Pelvic Floor Dysfunct*, 2000. 11: 156.
<https://www.ncbi.nlm.nih.gov/pubmed/11484743>
313. Oge, O., *et al.* Urothelium-preserving augmentation cystoplasty covered with a peritoneal flap. *BJU Int*, 2000. 85: 802.
<https://www.ncbi.nlm.nih.gov/pubmed/10792156>
314. Siracusano, S., *et al.* Laparoscopic bladder auto-augmentation in an incomplete traumatic spinal cord injury. *Spinal Cord*, 2000. 38: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/10762200>

315. Westney, O.L., *et al.* Surgical procedures for the treatment of urge incontinence. *Tech Urol*, 2001. 7: 126.
<https://www.ncbi.nlm.nih.gov/pubmed/11383990>
316. Zhang, F., *et al.* Sigmoidocolocystoplasty with ureteral reimplantation for treatment of neurogenic bladder. *Urology*, 2012. 80: 440.
<https://www.ncbi.nlm.nih.gov/pubmed/22857763>
317. Krebs, J., *et al.* Functional outcome of supratrigonal cystectomy and augmentation ileocystoplasty in adult patients with refractory neurogenic lower urinary tract dysfunction. *Neurourol Urodyn*, 2016. 35: 260.
<https://www.ncbi.nlm.nih.gov/pubmed/25524480>
318. Lima, D.X., *et al.* Quality of life evaluation of patients with neurogenic bladder submitted to reconstructive urological surgeries preserving the bladder. *Int Braz J Urol*, 2015. 41: 542.
<https://www.ncbi.nlm.nih.gov/pubmed/26200548>
319. Khavari, R., *et al.* A modification to augmentation cystoplasty with catheterizable stoma for neurogenic patients: technique and long-term results. *Urology*, 2012. 80: 460.
<https://www.ncbi.nlm.nih.gov/pubmed/22704181>
320. Hadley, D., *et al.* Creation of a continent urinary channel in adults with neurogenic bladder: long-term results with the Monti and Casale (Spiral Monti) procedures. *Urology*, 2014. 83: 1176.
<https://www.ncbi.nlm.nih.gov/pubmed/24612618>
321. Leslie, B., *et al.* Long-term followup and time to event outcome analysis of continent catheterizable channels. *J Urol*, 2011. 185: 2298.
<https://www.ncbi.nlm.nih.gov/pubmed/21511280>
322. Duckett, J.W., *et al.* Appendicovesicostomy (and variations) in bladder reconstruction. *J Urol*, 1993. 149: 567.
<https://www.ncbi.nlm.nih.gov/pubmed/8437267>
323. Kajbafzadeh, A.M., *et al.* Simultaneous Malone antegrade continent enema and Mitrofanoff principle using the divided appendix: report of a new technique for prevention of stoma complications. *J Urol*, 2001. 165: 2404.
<https://www.ncbi.nlm.nih.gov/pubmed/11371987>
324. Kawai, K., *et al.* Tissue-engineered artificial urothelium. *World J Surg*, 2000. 24: 1160.
<https://www.ncbi.nlm.nih.gov/pubmed/11071451>
325. Liard, A., *et al.* The Mitrofanoff procedure: 20 years later. *J Urol*, 2001. 165: 2394.
<https://www.ncbi.nlm.nih.gov/pubmed/11371985>
326. Moreno, J.G., *et al.* Improved quality of life and sexuality with continent urinary diversion in quadriplegic women with umbilical stoma. *Arch Phys Med Rehabil*, 1995. 76: 758.
<https://www.ncbi.nlm.nih.gov/pubmed/7632132>
327. Sekar, P., *et al.* Comparison of long-term renal function after spinal cord injury using different urinary management methods. *Arch Phys Med Rehabil*, 1997. 78: 992.
<https://www.ncbi.nlm.nih.gov/pubmed/9305274>
328. Stein, R., *et al.* Urinary diversion and orthotopic bladder substitution in children and young adults with neurogenic bladder: a safe option for treatment? *J Urol*, 2000. 163: 568.
<https://www.ncbi.nlm.nih.gov/pubmed/10647686>
329. Sylora, J.A., *et al.* Intermittent self-catheterization by quadriplegic patients via a catheterizable Mitrofanoff channel. *J Urol*, 1997. 157: 48.
<https://www.ncbi.nlm.nih.gov/pubmed/8976213>
330. Van Savage, J.G., *et al.* Transverse retubularized sigmoidovesicostomy continent urinary diversion to the umbilicus. *J Urol*, 2001. 166: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/11458110>
331. Karsenty, G., *et al.* A novel technique to achieve cutaneous continent urinary diversion in spinal cord-injured patients unable to catheterize through native urethra. *Spinal Cord*, 2008. 46: 305.
<https://www.ncbi.nlm.nih.gov/pubmed/17700513>
332. Peterson, A.C., *et al.* Urinary diversion in patients with spinal cord injury in the United States. *Urology*, 2012. 80: 1247.
<https://www.ncbi.nlm.nih.gov/pubmed/23206770>
333. Vanni, A.J., *et al.* Ileovesicostomy for the neurogenic bladder patient: outcome and cost comparison of open and robotic assisted techniques. *Urology*, 2011. 77: 1375.
<https://www.ncbi.nlm.nih.gov/pubmed/21146864>
334. Wiener, J.S., *et al.* Bladder augmentation versus urinary diversion in patients with spina bifida in the United States. *J Urol*, 2011. 186: 161.
<https://www.ncbi.nlm.nih.gov/pubmed/21575969>

335. Atan, A., *et al.* Advantages and risks of ileovesicostomy for the management of neuropathic bladder. *Urology*, 1999. 54: 636.
<https://www.ncbi.nlm.nih.gov/pubmed/10510920>
336. Cass, A.S., *et al.* A 22-year followup of ileal conduits in children with a neurogenic bladder. *J Urol*, 1984. 132: 529.
<https://www.ncbi.nlm.nih.gov/pubmed/6471190>
337. Hald, T., *et al.* Vesicostomy--an alternative urine diversion operation. Long term results. *Scand J Urol Nephrol*, 1978. 12: 227.
<https://www.ncbi.nlm.nih.gov/pubmed/725543>
338. Schwartz, S.L., *et al.* Incontinent ileo-vesicostomy urinary diversion in the treatment of lower urinary tract dysfunction. *J Urol*, 1994. 152: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/8201699>
339. Sakhri, R., *et al.* [Laparoscopic cystectomy and ileal conduit urinary diversion for neurogenic bladders and related conditions. Morbidity and better quality of life]. *Prog Urol*, 2015. 25: 342.
<https://www.ncbi.nlm.nih.gov/pubmed/25726693>
340. Herschorn, S., *et al.* Urinary undiversion in adults with myelodysplasia: long-term followup. *J Urol*, 1994. 152: 329.
<https://www.ncbi.nlm.nih.gov/pubmed/8015064>
341. Mukai, S., *et al.* Retrospective study for risk factors for febrile UTI in spinal cord injury patients with routine concomitant intermittent catheterization in outpatient settings. *Spinal Cord*, 2016. 54: 69.
<https://www.ncbi.nlm.nih.gov/pubmed/26458969>
342. Vasudeva, P., *et al.* Factors implicated in pathogenesis of urinary tract infections in neurogenic bladders: some revered, few forgotten, others ignored. *Neurourol Urodyn*, 2014. 33: 95.
<https://www.ncbi.nlm.nih.gov/pubmed/23460489>
343. Bakke, A., *et al.* Bacteriuria in patients treated with clean intermittent catheterization. *Scand J Infect Dis*, 1991. 23: 577.
<https://www.ncbi.nlm.nih.gov/pubmed/1767253>
344. Waites, K.B., *et al.* Epidemiology and risk factors for urinary tract infection following spinal cord injury. *Arch Phys Med Rehabil*, 1993. 74: 691.
<https://www.ncbi.nlm.nih.gov/pubmed/8328888>
345. Nicolle, L.E., *et al.* Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis*, 2005. 40: 643.
<https://www.ncbi.nlm.nih.gov/pubmed/15714408>
346. Goetz, L.L., *et al.* International Spinal Cord Injury Urinary Tract Infection Basic Data Set. *Spinal Cord*, 2013. 51: 700.
<https://www.ncbi.nlm.nih.gov/pubmed/23896666>
347. Pannek, J. Treatment of urinary tract infection in persons with spinal cord injury: guidelines, evidence, and clinical practice. A questionnaire-based survey and review of the literature. *J Spinal Cord Med*, 2011. 34: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/21528621>
348. Deville, W.L., *et al.* The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urol*, 2004. 4: 4.
<https://www.ncbi.nlm.nih.gov/pubmed/15175113>
349. Hoffman, J.M., *et al.* Nitrite and leukocyte dipstick testing for urinary tract infection in individuals with spinal cord injury. *J Spinal Cord Med*, 2004. 27: 128.
<https://www.ncbi.nlm.nih.gov/pubmed/15162883>
350. Biering-Sorensen, F., *et al.* Urinary tract infections in patients with spinal cord lesions: treatment and prevention. *Drugs*, 2001. 61: 1275.
<https://www.ncbi.nlm.nih.gov/pubmed/11511022>
351. Everaert, K., *et al.* Urinary tract infections in spinal cord injury: prevention and treatment guidelines. *Acta Clin Belg*, 2009. 64: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/19810421>
352. D'Hondt, F., *et al.* Urinary tract infections in patients with spinal cord injuries. *Curr Infect Dis Rep*, 2011. 13: 544.
<https://www.ncbi.nlm.nih.gov/pubmed/21853416>
353. Jia, C., *et al.* Detrusor botulinum toxin A injection significantly decreased urinary tract infection in patients with traumatic spinal cord injury. *Spinal Cord*, 2013. 51: 487.
<https://www.ncbi.nlm.nih.gov/pubmed/23357928>

354. Li, L., *et al.* Impact of hydrophilic catheters on urinary tract infections in people with spinal cord injury: systematic review and meta-analysis of randomized controlled trials. *Arch Phys Med Rehabil*, 2013. 94: 782.
<https://www.ncbi.nlm.nih.gov/pubmed/23168400>
355. Waites, K.B., *et al.* Evaluation of 3 methods of bladder irrigation to treat bacteriuria in persons with neurogenic bladder. *J Spinal Cord Med*, 2006. 29: 217.
<https://www.ncbi.nlm.nih.gov/pubmed/16859225>
356. Gallien, P., *et al.* Cranberry versus placebo in the prevention of urinary infections in multiple sclerosis: a multicenter, randomized, placebo-controlled, double-blind trial. *Mult Scler*, 2014. 20: 1252.
<https://www.ncbi.nlm.nih.gov/pubmed/24402038>
357. Lee, B.S., *et al.* Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev*, 2012. 10: Cd003265.
<https://www.ncbi.nlm.nih.gov/pubmed/23076896>
358. Günther, M., *et al.* Harnwegsinfektprophylaxe. Urinansäuerung mittels L-Methionin bei neurogener Blasenfunktionsstörung. *Urologe B*, 2002. 42: 218.
<http://link.springer.com/article/10.1007/s00131-002-0207-x>
359. Hachen, H.J. Oral immunotherapy in paraplegic patients with chronic urinary tract infections: a double-blind, placebo-controlled trial. *J Urol*, 1990. 143: 759.
<https://www.ncbi.nlm.nih.gov/pubmed/2179584>
360. Poirier, C., *et al.* Prevention of urinary tract infections by antibiotic cycling in spinal cord injury patients and low emergence of multidrug resistant bacteria. *Medecine et Maladies Infectieuses*, 2016. 16: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/27321478>
361. Darouiche, R.O., *et al.* Multicenter randomized controlled trial of bacterial interference for prevention of urinary tract infection in patients with neurogenic bladder. *Urology*, 2011. 78: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/21683991>
362. Pannek, J., *et al.* Usefulness of classical homoeopathy for the prevention of urinary tract infections in patients with neurogenic bladder dysfunction: A case series. *Indian J Res Homoeopathy*, 2014. 8: 31.
<http://www.ijrh.org/text.asp?2014/8/1/31/129675>
363. Rees, P.M., *et al.* Sexual function in men and women with neurological disorders. *Lancet*, 2007. 369: 512.
<https://www.ncbi.nlm.nih.gov/pubmed/17292771>
364. Lombardi, G., *et al.* Management of sexual dysfunction due to central nervous system disorders: A systematic review. *BJU International*, 2015. 115: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/25599613>
365. Jungwirth, A., *et al.*, EAU Guidelines on Male Infertility. In: *EAU Guidelines*, 2017 edition presented at the annual EAU Congress London 2017. ISBN 978-90-79754-91-5.
366. Hatzimouratidis, K., *et al.*, EAU guidelines on Male Sexual Dysfunction. In: *EAU Guidelines*, 2017 edition presented at the annual EAU Congress London 2017. ISBN 978-90-79754-91-5.
367. Foley, F.W., Sexuality. In: *Multiple Sclerosis: A Guide for Families*. Kalb, R.C., Editor. Demos Medical Publishing, 2006. New York, USA.
368. Annon, J.S., PLISSIT Therapy. In: *Handbook of Innovative Psychotherapies*. Corsini, R., Editor. Wiley & Sons, 1981. New York, USA.
369. Fragala, E., *et al.* Relationship between urodynamic findings and sexual function in multiple sclerosis patients with lower urinary tract dysfunction. *Eur J Neurol*, 2015. 22: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/25410608>
370. Game, X., *et al.* Sexual function of young women with myelomeningocele. *J Pediatr Urol*, 2014. 10: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/23992838>
371. 't Hoen, A., *et al.* A Quality Assessment of Patient-Reported Outcome Measures for Sexual Function in Neurologic Patients Using the Consensus-based Standards for the Selection of Health Measurement Instruments Checklist: A Systematic Review. *European Urology Focus*, 2016.
[http://www.europeanurology.com/article/S2405-4569\(16\)30069-4/abstract/](http://www.europeanurology.com/article/S2405-4569(16)30069-4/abstract/)
372. Lombardi, G., *et al.* Treatments for erectile dysfunction in spinal cord patients: alternatives to phosphodiesterase type 5 inhibitors? A review study. *Spinal Cord*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26193811>

373. Chen, L., *et al.* Phosphodiesterase 5 Inhibitors for the Treatment of Erectile Dysfunction: A Trade-off Network Meta-analysis. *Eur Urol*, 2015. 68: 674.
<https://www.ncbi.nlm.nih.gov/pubmed/25817916>
374. Lombardi, G., *et al.* Ten years of phosphodiesterase type 5 inhibitors in spinal cord injured patients. *J Sex Med*, 2009. 6: 1248.
<https://www.ncbi.nlm.nih.gov/pubmed/19210710>
375. Lombardi, G., *et al.* Treating erectile dysfunction and central neurological diseases with oral phosphodiesterase type 5 inhibitors. Review of the literature. *J Sex Med*, 2012. 9: 970.
<https://www.ncbi.nlm.nih.gov/pubmed/22304626>
376. Cardenas, D.D., *et al.* Two phase 3, multicenter, randomized, placebo-controlled clinical trials of fampridine-SR for treatment of spasticity in chronic spinal cord injury. *Spinal Cord*, 2014. 52: 70.
<https://www.ncbi.nlm.nih.gov/pubmed/24216616>
377. Strelbel, R.T., *et al.* Apomorphine sublingual as primary or secondary treatment for erectile dysfunction in patients with spinal cord injury. *BJU Int*, 2004. 93: 100.
<https://www.ncbi.nlm.nih.gov/pubmed/14678378>
378. Pohanka, M., *et al.* The long-lasting improvement of sexual dysfunction in patients with advanced, fluctuating Parkinson's disease induced by pergolide: evidence from the results of an open, prospective, one-year trial. *Parkinsonism Relat Disord*, 2005. 11: 509.
<https://www.ncbi.nlm.nih.gov/pubmed/15994112>
379. Chancellor, M.B., *et al.* Prospective comparison of topical minoxidil to vacuum constriction device and intracorporeal papaverine injection in treatment of erectile dysfunction due to spinal cord injury. *Urology*, 1994. 43: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/8134992>
380. Cookson, M.S., *et al.* Long-term results with vacuum constriction device. *J Urol*, 1993. 149: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/8426404>
381. Denil, J., *et al.* Vacuum erection device in spinal cord injured men: patient and partner satisfaction. *Arch Phys Med Rehabil*, 1996. 77: 750.
<https://www.ncbi.nlm.nih.gov/pubmed/8702367>
382. Levine, L.A. External devices for treatment of erectile dysfunction. *Endocrine*, 2004. 23: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/15146095>
383. Levine, L.A., *et al.* Vacuum constriction and external erection devices in erectile dysfunction. *Urol Clin North Am*, 2001. 28: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/11402585>
384. Bella, A.J., *et al.* Intracavernous pharmacotherapy for erectile dysfunction. *Endocrine*, 2004. 23: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/15146094>
385. Bodner, D.R., *et al.* The application of intracavernous injection of vasoactive medications for erection in men with spinal cord injury. *J Urol*, 1987. 138: 310.
<https://www.ncbi.nlm.nih.gov/pubmed/3599245>
386. Dinsmore, W.W., *et al.* Treating men with predominantly nonpsychogenic erectile dysfunction with intracavernosal vasoactive intestinal polypeptide and phentolamine mesylate in a novel auto-injector system: a multicentre double-blind placebo-controlled study. *BJU Int*, 1999. 83: 274.
<https://www.ncbi.nlm.nih.gov/pubmed/10233493>
387. Hirsch, I.H., *et al.* Use of intracavernous injection of prostaglandin E1 for neuropathic erectile dysfunction. *Paraplegia*, 1994. 32: 661.
<https://www.ncbi.nlm.nih.gov/pubmed/7831071>
388. Kapoor, V.K., *et al.* Intracavernous papaverine for impotence in spinal cord injured patients. *Paraplegia*, 1993. 31: 675.
<https://www.ncbi.nlm.nih.gov/pubmed/8259331>
389. Vidal, J., *et al.* Intracavernous pharmacotherapy for management of erectile dysfunction in multiple sclerosis patients. *Rev Neurol*, 1995. 23: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/7497173>
390. Deforge, D., *et al.* Male erectile dysfunction following spinal cord injury: a systematic review. *Spinal Cord*, 2006. 44: 465.
<https://www.ncbi.nlm.nih.gov/pubmed/16317419>
391. Bodner, D.R., *et al.* Intraurethral alprostadil for treatment of erectile dysfunction in patients with spinal cord injury. *Urology*, 1999. 53: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/9886612>
392. Gross, A.J., *et al.* Penile prostheses in paraplegic men. *Br J Urol*, 1996. 78: 262.
<https://www.ncbi.nlm.nih.gov/pubmed/8813925>
393. Kimoto, Y., *et al.* Penile prostheses for the management of the neuropathic bladder and sexual

- dysfunction in spinal cord injury patients: long term follow up. *Paraplegia*, 1994. 32: 336.
<https://www.ncbi.nlm.nih.gov/pubmed/8058351>
394. Zermann, D.H., *et al.* Penile prosthetic surgery in neurologically impaired patients: long-term followup. *J Urol*, 2006. 175: 1041.
<https://www.ncbi.nlm.nih.gov/pubmed/16469612>
395. Fode, M., *et al.* Male sexual dysfunction and infertility associated with neurological disorders. *Asian J Androl*, 2012. 14: 61.
<https://www.ncbi.nlm.nih.gov/pubmed/22138899>
396. Lim, T.C., *et al.* A simple technique to prevent retrograde ejaculation during assisted ejaculation. *Paraplegia*, 1994. 32: 142.
<https://www.ncbi.nlm.nih.gov/pubmed/8008416>
397. Philippon, M., *et al.* Successful pregnancies and healthy live births using frozen-thawed sperm retrieved by a new modified Hotchkiss procedure in males with retrograde ejaculation: first case series. *Basic Clin Androl*, 2015. 25: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/26034605>
398. Arafa, M.M., *et al.* Prostatic massage: a simple method of semen retrieval in men with spinal cord injury. *Int J Androl*, 2007. 30: 170.
<https://www.ncbi.nlm.nih.gov/pubmed/17298549>
399. Kolettis, P.N., *et al.* Fertility outcomes after electroejaculation in men with spinal cord injury. *Fertil Steril*, 2002. 78: 429.
<https://www.ncbi.nlm.nih.gov/pubmed/12137889>
400. Chehensse, C., *et al.* The spinal control of ejaculation revisited: a systematic review and meta-analysis of anejaculation in spinal cord injured patients. *Hum Reprod Update*, 2013. 19: 507.
<https://www.ncbi.nlm.nih.gov/pubmed/23820516>
401. Beretta, G., *et al.* Reproductive aspects in spinal cord injured males. *Paraplegia*, 1989. 27: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/2717193>
402. Brackett, N.L., *et al.* Application of 2 vibrators salvages ejaculatory failures to 1 vibrator during penile vibratory stimulation in men with spinal cord injuries. *J Urol*, 2007. 177: 660.
<https://www.ncbi.nlm.nih.gov/pubmed/17222653>
403. Sonksen, J., *et al.* Ejaculation induced by penile vibratory stimulation in men with spinal cord injuries. The importance of the vibratory amplitude. *Paraplegia*, 1994. 32: 651.
<https://www.ncbi.nlm.nih.gov/pubmed/7831070>
404. Claydon, V.E., *et al.* Cardiovascular responses to vibrostimulation for sperm retrieval in men with spinal cord injury. *J Spinal Cord Med*, 2006. 29: 207.
<https://www.ncbi.nlm.nih.gov/pubmed/16859224>
405. Eklund, M.B., *et al.* Incidence of autonomic dysreflexia and silent autonomic dysreflexia in men with spinal cord injury undergoing sperm retrieval: implications for clinical practice. *J Spinal Cord Med*, 2008. 31: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/18533409>
406. Soler, J.M., *et al.* Midodrine improves ejaculation in spinal cord injured men. *J Urol*, 2007. 178: 2082.
<https://www.ncbi.nlm.nih.gov/pubmed/17869290>
407. Pecori, C., *et al.* Paternal therapy with disease modifying drugs in multiple sclerosis and pregnancy outcomes: a prospective observational multicentric study. *BMC Neurol*, 2014. 14: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/24884599>
408. Brackett, N.L., *et al.* Treatment of infertility in men with spinal cord injury. *Nat Rev Urol*, 2010. 7: 162.
<https://www.ncbi.nlm.nih.gov/pubmed/20157304>
409. Raviv, G., *et al.* Testicular sperm retrieval and intra cytoplasmic sperm injection provide favorable outcome in spinal cord injury patients, failing conservative reproductive treatment. *Spinal Cord*, 2013. 51: 642.
<https://www.ncbi.nlm.nih.gov/pubmed/23689394>
410. Schatte, E.C., *et al.* Treatment of infertility due to anejaculation in the male with electroejaculation and intracytoplasmic sperm injection. *J Urol*, 2000. 163: 1717.
<https://www.ncbi.nlm.nih.gov/pubmed/10799167>
411. Shieh, J.Y., *et al.* A protocol of electroejaculation and systematic assisted reproductive technology achieved high efficiency and efficacy for pregnancy for anejaculatory men with spinal cord injury. *Arch Phys Med Rehabil*, 2003. 84: 535.
<https://www.ncbi.nlm.nih.gov/pubmed/12690592>

412. Taylor, Z., *et al.* Contribution of the assisted reproductive technologies to fertility in males suffering spinal cord injury. *Aust N Z J Obstet Gynaecol*, 1999. 39: 84.
<https://www.ncbi.nlm.nih.gov/pubmed/10099757>
413. Rutkowski, S.B., *et al.* The influence of bladder management on fertility in spinal cord injured males. *Paraplegia*, 1995. 33: 263.
<https://www.ncbi.nlm.nih.gov/pubmed/7630651>
414. Hamed, S.A., *et al.* Seminal fluid analysis and testicular volume in adults with epilepsy receiving valproate. *J Clin Neurosci*, 2015. 22: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/25636832>
415. Ohl, D.A., *et al.* Electroejaculation versus vibratory stimulation in spinal cord injured men: sperm quality and patient preference. *J Urol*, 1997. 157: 2147.
<https://www.ncbi.nlm.nih.gov/pubmed/9146603>
416. Brackett, N.L., *et al.* Semen quality of spinal cord injured men is better when obtained by vibratory stimulation versus electroejaculation. *J Urol*, 1997. 157: 151.
<https://www.ncbi.nlm.nih.gov/pubmed/8976239>
417. Brackett, N.L., *et al.* Semen retrieval in men with spinal cord injury is improved by interrupting current delivery during electroejaculation. *J Urol*, 2002. 167: 201.
<https://www.ncbi.nlm.nih.gov/pubmed/11743305>
418. DeForge, D., *et al.* Fertility following spinal cord injury: a systematic review. *Spinal Cord*, 2005. 43: 693.
<https://www.ncbi.nlm.nih.gov/pubmed/15951744>
419. Ferreira-Velasco, M.E., *et al.* Sexual issues in a sample of women with spinal cord injury. *Spinal Cord*, 2005. 43: 51.
<https://www.ncbi.nlm.nih.gov/pubmed/15303115>
420. Kreuter, M., *et al.* Sexuality and sexual life in women with spinal cord injury: a controlled study. *J Rehabil Med*, 2008. 40: 61.
<https://www.ncbi.nlm.nih.gov/pubmed/18176739>
421. Kreuter, M., *et al.* Sexual adjustment and quality of relationship in spinal paraplegia: a controlled study. *Arch Phys Med Rehabil*, 1996. 77: 541.
<https://www.ncbi.nlm.nih.gov/pubmed/8831469>
422. Kessler, T.M., *et al.* Sexual dysfunction in multiple sclerosis. *Expert Rev Neurother*, 2009. 9: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/19271943>
423. Lew-Starowicz, M., *et al.* Prevalence of Sexual Dysfunctions Among Women with Multiple Sclerosis. *Sex Disabil*, 2013. 31: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/23704801>
424. Reitz, A., *et al.* Impact of spinal cord injury on sexual health and quality of life. *Int J Impot Res*, 2004. 16: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/14973522>
425. Harrison, J., *et al.* Factors associated with sexual functioning in women following spinal cord injury. *Paraplegia*, 1995. 33: 687.
<https://www.ncbi.nlm.nih.gov/pubmed/8927405>
426. Westgren, N., *et al.* Sexuality in women with traumatic spinal cord injury. *Acta Obstet Gynecol Scand*, 1997. 76: 977.
<https://www.ncbi.nlm.nih.gov/pubmed/9435740>
427. Lombardi, G., *et al.* Management of sexual dysfunction due to central nervous system disorders: a systematic review. *BJU Int*, 2015. 115 Suppl 6: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/25599613>
428. Fruhauf, S., *et al.* Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis. *Arch Sex Behav*, 2013. 42: 915.
<https://www.ncbi.nlm.nih.gov/pubmed/23559141>
429. Alexander, M., *et al.* Spinal cord injuries and orgasm: a review. *J Sex Marital Ther*, 2008. 34: 308.
<https://www.ncbi.nlm.nih.gov/pubmed/18576233>
430. Sipski, M.L., *et al.* Sexual arousal and orgasm in women: effects of spinal cord injury. *Ann Neurol*, 2001. 49: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/11198294>
431. Sipski, M.L., *et al.* Physiologic parameters associated with sexual arousal in women with incomplete spinal cord injuries. *Arch Phys Med Rehabil*, 1997. 78: 305.
<https://www.ncbi.nlm.nih.gov/pubmed/9084355>

432. McAlonan, S. Improving sexual rehabilitation services: the patient's perspective. *Am J Occup Ther*, 1996. 50: 826.
<https://www.ncbi.nlm.nih.gov/pubmed/8947375>
433. Schopp, L.H., *et al.* Impact of comprehensive gynecologic services on health maintenance behaviours among women with spinal cord injury. *Disabil Rehabil*, 2002. 24: 899.
<https://www.ncbi.nlm.nih.gov/pubmed/12519485>
434. Sukumaran, S.C., *et al.* Polytherapy increases the risk of infertility in women with epilepsy. *Neurology*, 2010. 75: 1351.
<https://www.ncbi.nlm.nih.gov/pubmed/20938026>
435. Axel, S.J. Spinal cord injured women's concerns: menstruation and pregnancy. *Rehabil Nurs*, 1982. 7: 10.
<https://www.ncbi.nlm.nih.gov/pubmed/6921826>
436. Jackson, A.B., *et al.* A multicenter study of women's self-reported reproductive health after spinal cord injury. *Arch Phys Med Rehabil*, 1999. 80: 1420.
<https://www.ncbi.nlm.nih.gov/pubmed/10569436>
437. Baker, E.R., *et al.* Pregnancy in spinal cord injured women. *Arch Phys Med Rehabil*, 1996. 77: 501.
<https://www.ncbi.nlm.nih.gov/pubmed/8629929>
438. Baker, E.R., *et al.* Risks associated with pregnancy in spinal cord-injured women. *Obstet Gynecol*, 1992. 80: 425.
<https://www.ncbi.nlm.nih.gov/pubmed/1495699>
439. Cross, L.L., *et al.* Pregnancy, labor and delivery post spinal cord injury. *Paraplegia*, 1992. 30: 890.
<https://www.ncbi.nlm.nih.gov/pubmed/1287543>
440. Hughes, S.J., *et al.* Management of the pregnant woman with spinal cord injuries. *Br J Obstet Gynaecol*, 1991. 98: 513.
<https://www.ncbi.nlm.nih.gov/pubmed/1873238>
441. Dannels, A., *et al.* The perimenopause experience for women with spinal cord injuries. *SCI Nurs*, 2004. 21: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/15176344>
442. Vukusic, S., *et al.* Multiple sclerosis and pregnancy in the 'treatment era'. *Nat Rev Neurol*, 2015. 11: 280.
<https://www.ncbi.nlm.nih.gov/pubmed/15176344>
443. Bove, R., *et al.* Management of multiple sclerosis during pregnancy and the reproductive years: a systematic review. *Obstet Gynecol*, 2014. 124: 1157.
<https://www.ncbi.nlm.nih.gov/pubmed/25415167>
444. Pannek, J., *et al.* Clinical usefulness of ultrasound assessment of detrusor wall thickness in patients with neurogenic lower urinary tract dysfunction due to spinal cord injury: Urodynamics made easy? *World J Urol*, 2013. 31: 659.
<https://www.ncbi.nlm.nih.gov/pubmed/23073657>
445. Silva, J.A., *et al.* Association between the bladder wall thickness and urodynamic findings in patients with spinal cord injury. *World J Urol*, 2015. 33: 131.
<https://www.ncbi.nlm.nih.gov/pubmed/24573904>
446. Veenboer, P.W., *et al.* Diagnostic accuracy of Tc-99m DMSA scintigraphy and renal ultrasonography for detecting renal scarring and relative function in patients with spinal dysraphism. *Neurourol Urodyn*, 2015. 34: 513.
<https://www.ncbi.nlm.nih.gov/pubmed/24706504>

5. CONFLICT OF INTEREST

All members of the EAU Neuro-urology Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: <http://www.uroweb.org/guidelines/>. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Erectile Dysfunction, Premature Ejaculation, Penile Curvature and Priapism

K. Hatzimouratidis (Chair), F. Giuliano, I. Moncada,
A. Muneer, A. Salonia (Vice-chair), P. Verze
Guideline Associates: A. Parnham, E.C. Serefoglu

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1. INTRODUCTION

1.1 Aim

These guidelines include four sections. The aim of the first two sections is to present the current evidence for the diagnosis and treatment of patients suffering from erectile dysfunction (ED) and premature ejaculation (PE). Erectile Dysfunction and PE are the two main complaints in male sexual medicine [1, 2]. Pharmacological therapies have completely changed the diagnostic and therapeutic approach to ED.

The aim of the third section is to provide the practicing urologist with the most recent evidence on the diagnosis and management of penile curvature in order to assist in their decision-making. Penile curvature is a common urological disorder which can be congenital or acquired. Congenital curvature is briefly discussed in these guidelines as a distinct pathology in the adult population without any other concomitant abnormality present (such as urethral abnormalities). For paediatric congenital penile curvature, please refer to the EAU Guidelines on Paediatric Urology, Chapter on Congenital Penile Curvature [3]. Acquired curvature is mainly due to Peyronie's disease but can also be due to the development of fibrosis following penile fracture.

The aim of the fourth section is to present the current evidence for the diagnosis and treatment of patients suffering from priapism. Priapism is a pathological condition representing a true disorder of penile erection that persists for more than four hours and beyond, or is unrelated to, sexual interest or stimulation [4]. Overall, erections lasting up to four hours are by consensus defined as 'prolonged'. Priapism may occur at all ages. The incidence rate of priapism in the general population is low (0.5-0.9 cases per 100,000 person-years) [5, 6]. In men with sickle cell disease, the prevalence of priapism is up to 3.6% in men less than eighteen years of age [7] increasing up to 42% in men more than eighteen years of age [8-11].

The Guidelines Office of the European Association of Urology (EAU) has appointed an Expert Panel to update previously published EAU guidelines for ED, PE, penile curvature and priapism.

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guidelines recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not and should not purport to be a legal standard of care.

1.2 Publication history

The first EAU Guidelines on Erectile Dysfunction were published in 2000 with subsequent updates in 2001, 2002, 2004, 2005, 2009, 2013 and 2014. In particular, the 2009 document presented a significant update of the previous publication with the inclusion of the topic "Premature Ejaculation" and the text was renamed "EAU Guidelines on Male Sexual Dysfunction" [12]. In 2011 the Panel decided to develop new guidelines addressing Penile Curvature, which resulted in a new publication in 2012 [13]. In 2014 a guideline on Priapism was completed [14].

The 2016 edition merged the previous EAU guidelines for ED, PE, penile curvature and priapism into one guideline [15].

1.3 Available Publications

Alongside several scientific summaries published in the EAU scientific journal, *European Urology* [16-20], a quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Male Sexual Dysfunction guidelines. These are abridged versions which may require consultation together with the full text version. All available material can be viewed and downloaded at the EAU website, which also includes a selection of translations produced by national urological associations: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Panel composition

The EAU Guidelines Panel on Male Sexual Dysfunction consists of urologists. Members of this Panel have been selected based on their expertise to represent the professionals treating patients suffering from ED, PE, penile curvature and priapism.

2. METHODS

2.1 Introduction

References used in this text are assessed according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [21]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://www.uroweb.org/guidelines/>. A list of Associations endorsing the EAU Guidelines can also be reviewed online at the above address.

For the 2016 print, a scoping search was performed covering all areas of the guideline covering the period May 2015 to June 2016. Embase, Medline and the Cochrane Central Register of Controlled Trials (RCTs) databases were searched, with a limitation to systematic reviews, meta-analyses or randomised controlled trials. A total of 2,783 unique records were identified, retrieved and screened for relevance, of which 56 were selected for inclusion. A detailed search strategy is available online: <http://www.uroweb.org/guideline/male-sexual-dysfunction/>.

2.2 Review

This document was subject to peer review prior to publication in 2015.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2018 update of the Male Sexual Dysfunction Guidelines. Ongoing systematic reviews include:

1. What is the effectiveness (efficacy and safety) of non-operative treatment for Peyronie's disease?
2. What is the effectiveness (efficacy and safety) of surgical treatment for Peyronie's disease?
3. What are the benefits and harms of testosterone treatment for male sexual dysfunction? [22].

3. MALE SEXUAL DYSFUNCTION

3.1 Erectile dysfunction

3.1.1 *Epidemiology/aetiology/pathophysiology*

Penile erection is a complex phenomenon which implies a delicate and co-ordinated equilibrium among the neurological, vascular and the tissue compartments. It includes arterial dilation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism [23]. Erectile Dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [24]. Erectile Dysfunction may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners [25-27]. There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease. Erectile Dysfunction should not be regarded only as a Quality of Life (QoL), but also as a potential warning sign of cardiovascular disease (CVD) [28-30].

3.1.1.1 *Epidemiology*

Epidemiological data have shown a high prevalence and incidence of ED worldwide. Among others, the Massachusetts Male Aging Study (MMAS) [25] reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% [31]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [32] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [33]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients was younger than 40 years, with almost 50% of the young men complaining of severe ED [34]. Differences between these studies can be explained by differences in methodology, in the ages, and socio-economic and cultural status of the populations studied.

3.1.1.2 *Risk factors*

Erectile Dysfunction shares both unmodifiable and modifiable common risk factors with CVD (e.g., obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, lack of exercise, and smoking) [27, 35-37]. Recent reports confirmed the association between ED status and age, diabetes mellitus duration, poor glycemic control and body mass index (BMI) [38].

A number of studies have shown some evidence that lifestyle modification [29, 39] and pharmacotherapy [39, 40] for CVD risk factors may be of help in improving sexual function in men with ED. However, it should be emphasised that more controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in the prevention or treatment of ED [30].

Epidemiological studies have also demonstrated consistent evidence for an association between lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) and sexual dysfunction, regardless of age, other comorbidities and various lifestyle factors [41]. The Multinational Survey on the Aging Male (MSAM-7) study - performed in the US, France, Germany, Italy, Netherlands, Spain, and the UK - systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. From the 83% of men who self-reported to be sexually active, the overall prevalence of LUTS was 90%, with the overall prevalence of ED being 49%, and a reported complete absence of erection in 10% of patients. Moreover, the overall prevalence of ejaculatory disorders was 46% [42].

The most recent epidemiological data collection have also highlighted other unexpected risk factors potentially associated with ED including psoriasis [43], ankylosing spondylitis [44], non-alcoholic fatty liver [45], and transrectal ultrasound (TRUS)-guided prostate biopsy [46].

3.1.1.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 1) [23].

Table 1: Pathophysiology of ED

Vasculogenic
Cardiovascular disease (hypertension, coronary artery disease, peripheral vasculopathy, etc.)
Diabetes mellitus
Hyperlipidaemia
Smoking
Major pelvic surgery (radical prostatectomy (RP)) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
<i>Central causes</i>
Degenerative disorders (multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
Spinal cord trauma or diseases
Stroke
Central nervous system tumours
<i>Peripheral causes</i>
Type 1 and 2 diabetes mellitus
Chronic renal failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum)
Surgery of the urethra (urethral stricture, urethroplasty, etc.)
Anatomical or structural
Hypospadias, epispadias
Micropenis
Peyronie's disease
Penile cancer
Phimosis
Hormonal
Hypogonadism
Hyperprolactinaemia
Hyper- and hypothyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Drug-induced
Antihypertensives (thiazide diuretics, etc.)
Antidepressants (selective serotonin reuptake inhibitors, tricyclics)

Antipsychotics (neuroleptics, etc.)
Antiandrogens (GnRH analogues and antagonists)
Recreational drugs (alcohol, heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, etc.)
Psychogenic
Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fractures

3.1.1.3.1 Post-radical prostatectomy ED, post-radiotherapy ED & post-brachytherapy ED

Radical prostatectomy (RP) in any form (open, laparoscopic, or robotic) is a widely performed procedure for patients with clinically localised prostate cancer (PCa) and a life expectancy of at least ten years [47]. This procedure may lead to treatment-specific sequelae affecting health-related QoL. This outcome has become increasingly important with the more frequent diagnosis of PCa in younger men [48, 49]. Research has shown that 25-75% of men experience post-RP ED [50]. Of clinical relevance, the rate of unassisted post-operative erectile function recovery is in the range between 20 and 25% in most studies; (these rates emerged not to have been substantially improved or changed over the past seventeen years [51]. Given the growing clinical importance of robot-assisted RP (RARP), this type of surgery is becoming the paradigm for post-operative functional results. A systematic review (SR) has shown a significant advantage in favour of RARP in comparison with open retropubic RP in terms of 12-month potency rates [52], without significant differences between laparoscopic RP and RARP. Some recent reports confirm that the possibility of achieving erectile function recovery is about twice as high for the RARP compared with the open RP [53]. Recently a prospective, controlled, non-randomised trial of patients undergoing RP in fourteen Swedish centres comparing RARP versus retropubic RP, showed a small improvement regarding erectile function (EF) after RARP [54]. Conversely, a randomised controlled phase 3 study of men assigned to open RP or RARP showed that the two techniques yielded similar functional outcomes at twelve weeks [55]. As a whole, more controlled prospective studies, with longer term follow-up, are necessary to determine if RARP is superior to open RP in terms of post-operative ED rates [56]. Overall, patient age and surgical volume, with the consequent ability to preserve the neurovascular bundles, seem to be the main factors in promoting the highest rates of post-operative potency [48, 50].

Pre-operative potency is a major factor associated with the recovery of EF after surgery [49]. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [48, 49]. Overall, the chronological aspects are of major clinical importance in terms of post-operative recovery of erectile function. Available data confirm that post-operative erectile function recovery can also occur years following RP (up to 48 months) [57]. Likewise, it is shared opinion that the timing of post-operative therapy (any type) should be commenced as close as possible to the surgical procedure [48, 50].

Erectile Dysfunction is also a common sequela after external beam radiotherapy and brachytherapy for PCa [58, 59]. The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue [58]. Alternative treatments for PCa including cryotherapy and high-intensity focused ultrasound (HIFU) are also associated with equivalent or higher rates of ED compared to surgery or radiation therapy [60, 61].

3.1.1.3.2 Summary of evidence on the epidemiology/aetiology/pathophysiology of ED

Summary of evidence	LE
ED is common worldwide.	2b
ED shares common risk factors with cardiovascular disease.	2b
Lifestyle modification (regular exercise and decrease in body mass index) can improve erectile function.	1b
ED is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
ED is common after RP, irrespective of the surgical technique used.	2b
ED is common after external radiotherapy and brachytherapy.	2b
ED is common after cryotherapy and high-intensity focused US.	2b

3.1.2 **Classification**

Erectile Dysfunction is commonly classified into three categories based on its aetiology. These include organic, psychogenic and mixed ED. However, this classification should be used with caution since most cases are actually of mixed aetiology. It is therefore suggested to use the term primary organic or primary psychogenic.

3.1.3 **Diagnostic evaluation**

3.1.3.1 **Basic work-up**

The first step in evaluating ED is always a detailed medical and sexual history of patients and, when available, their partners [62]. In this context, taking a comprehensive medical history may reveal one of the many common disorders associated with ED [62]. It is important to establish a relaxed atmosphere during history-taking. This will make it easier to i) ask questions about erectile function and other aspects of the sexual history; and, ii) to explain the diagnosis and therapeutic approach to the patient and his partner. Figure 1 lists the minimal diagnostic evaluation (basic work-up) in patients with ED.

3.1.3.1.1 Sexual history

The sexual history must include information about sexual orientation, previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful.

A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and of problems with sexual desire, arousal, ejaculation, and orgasm [63, 64]. Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) [65] or its short version the Sexual Health Inventory for Men (SHIM) [66], help to assess the different sexual function domains (i.e. sexual desire, erectile function, orgasmic function, intercourse, and overall satisfaction), as well as the potential impact of a specific treatment modality.

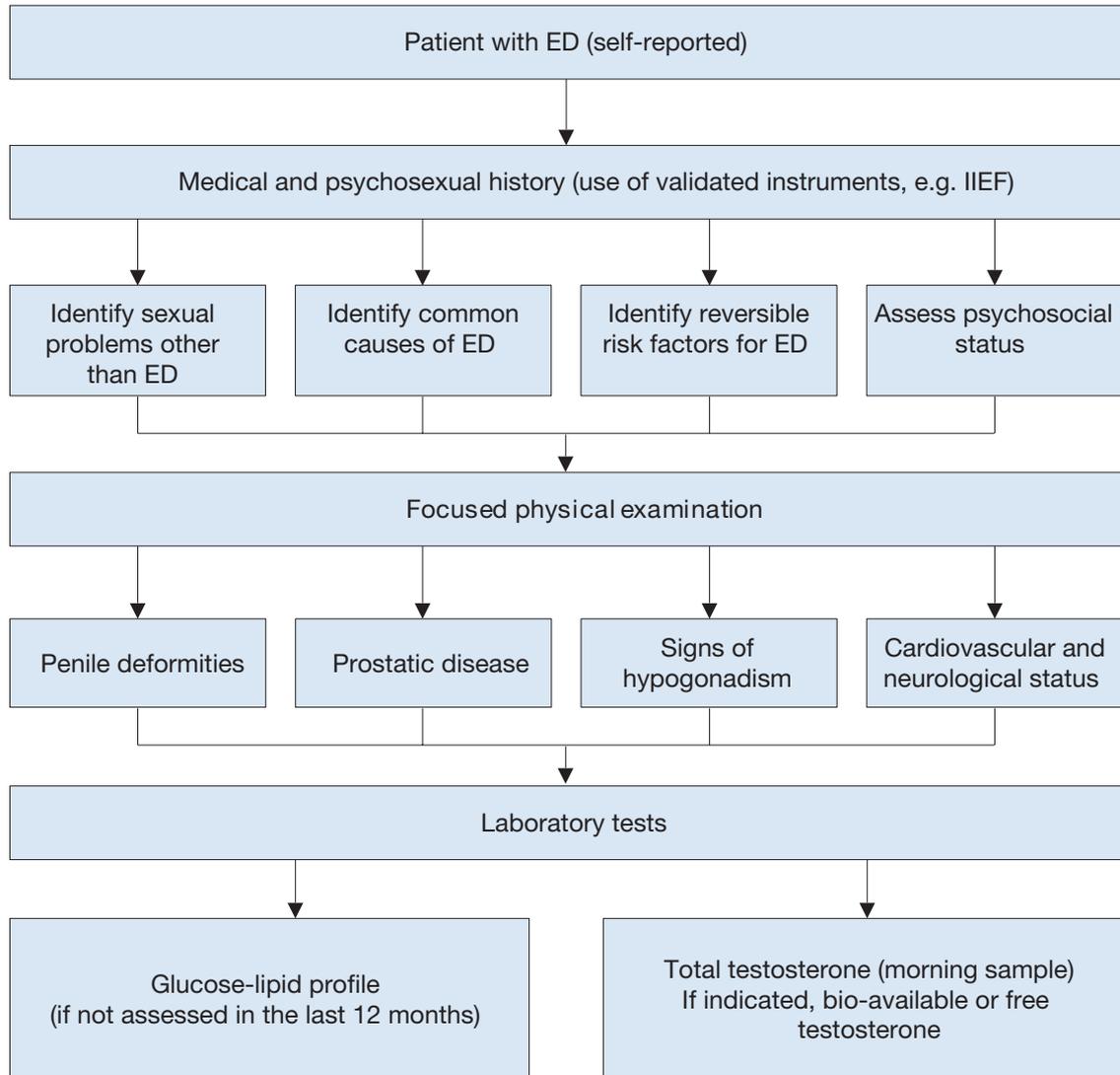
Psychometric analyses also support the use of the erectile hardness score for the assessment of penile rigidity in practice and in clinical trials research [67]. In cases of clinical depression, the use of a 2-question scale for depression is recommended in everyday clinical practice: "During the past month have you often been bothered by feeling down, depressed or hopeless? During the past month have you often been bothered by little interest or pleasure, doing things?" [68]. Patients should always be screened for symptoms of possible hypogonadism (= testosterone deficiency), including decreased energy, libido, fatigue and cognitive impairment, as well as for LUTS. In this regard, although LUTS/BPH in itself does not represent a contraindication to treat a patient for late onset hypogonadism, screening for LUTS severity is clinically relevant [69].

3.1.3.1.2 Physical examination

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems [70, 71]. A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggesting hypogonadism (small testes, alterations in secondary sexual characteristics etc.). Blood pressure and heart rate should be measured if they have not been assessed in the previous three to six months. Likewise either BMI calculation or waist circumference measurement should be taken into consideration in every patient with comorbid conditions.

3.1.3.1.3 Laboratory testing

Laboratory testing must be tailored to the patient's complaints and risk factors. Patients may need a fasting blood glucose or HbA1c and lipid profile if they have not recently been assessed. Hormonal tests include an early morning total testosterone. If indicated, the bio-available or calculated-free testosterone may be needed to corroborate total testosterone measurements. However, the threshold of testosterone required to maintain an erection is low and ED is usually a symptom of more severe cases of hypogonadism [35, 72-74]. For levels > 8 nmol/l the relationship between circulating testosterone and sexual functioning is very low [35, 72-74]. Additional laboratory tests may be considered in selected patients (e.g., prostate-specific antigen (PSA) [75]; prolactin, and luteinising hormone [76]. Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, these present opportunities to identify critical comorbid conditions that should not be missed [71].

Figure 1: Minimal diagnostic evaluation (basic work-up) in patients with ED

ED = erectile dysfunction; IIEF = International Index of Erectile Function.

3.1.3.1.4 Cardiovascular system and sexual activity: the patient at risk

Patients who seek treatment for sexual dysfunction have a high prevalence of CVDs. Epidemiological surveys have emphasised the association between cardiovascular and metabolic risk factors and sexual dysfunction in both men [77] and women [78]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [79, 80]. ED significantly increases the risk of CVD, coronary heart disease, stroke, and all these cause mortality, and the increase is probably independent of conventional cardiovascular risk factors [28, 29, 81]. Longitudinal data from an observational population-based study of 965 men without CVD, showed that younger men (< 50 years) with persistent ED have an increased Framingham risk that is independent of traditional CVD risk factors [82].

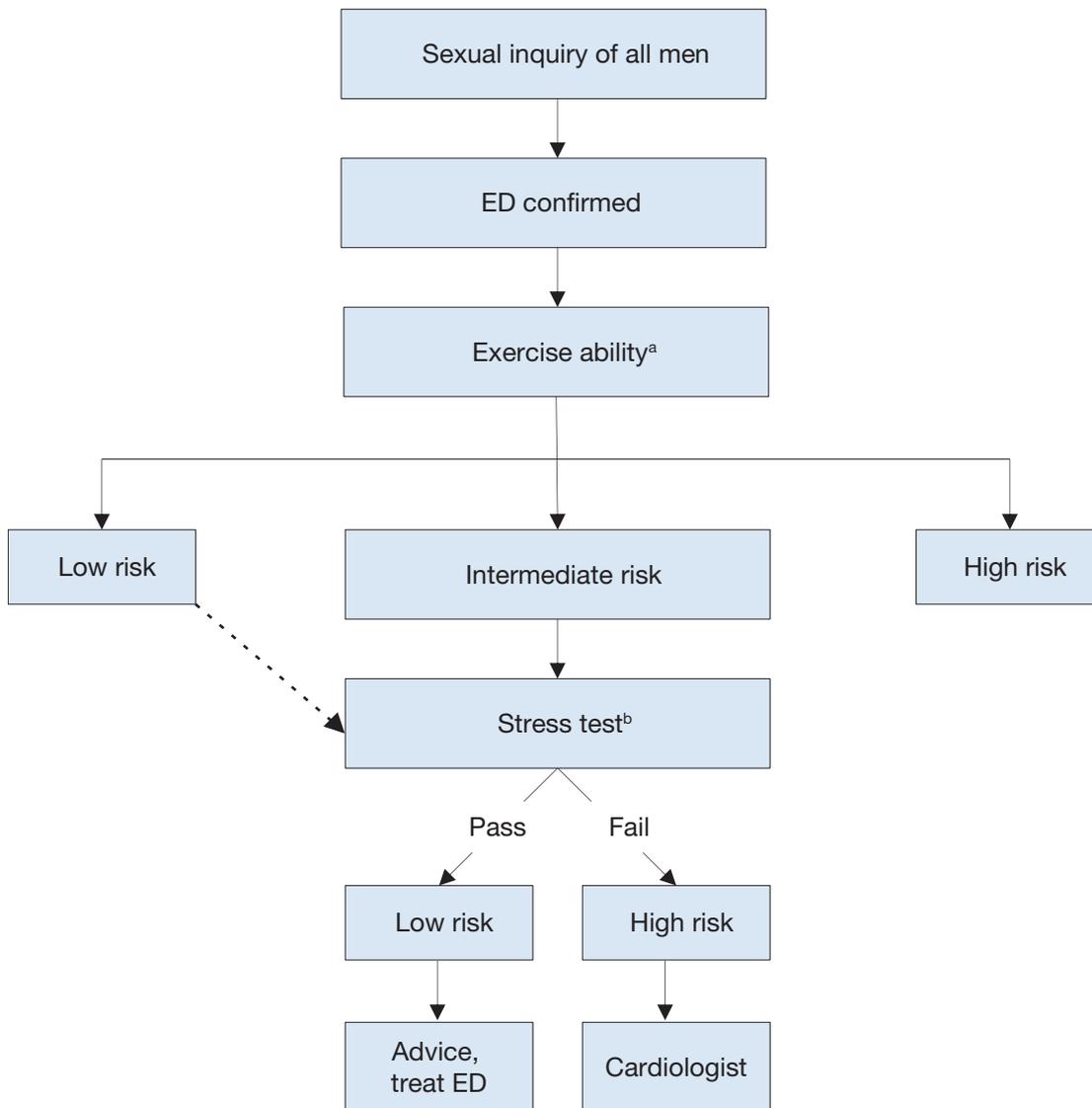
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [83]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [83-85]. Accordingly, patients with ED can be stratified into three cardiovascular risk categories (Table 2), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 2). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, which can be determined when taking the patient's history [40].

Table 2: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus [83, 85])

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Figure 2: Treatment algorithm for determining level of sexual activity according to cardiac risk in Erectile Dysfunction (based on 3rd Princeton Consensus) [83]



^a Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.

^b Sexual activity is equivalent to four minutes of the Bruce treadmill protocol.

3.1.3.1.4.1 Low-risk category

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low-risk is typically implied by the ability to perform exercise of modest intensity, which is defined as, ≥ 6 metabolic equivalents of energy expenditure in the resting state without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before the initiation or resumption of sexual activity or therapy for sexual dysfunction.

3.1.3.1.4.2 Intermediate- or indeterminate-risk category

The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

3.1.3.1.4.3 High-risk category

High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderate-to-severe symptomatic heart disease. High-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient's cardiac condition has been stabilised by treatment, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

3.1.3.2 *Specialised diagnostic tests*

Most patients with ED can be managed within the sexual care setting; conversely, some patients may need specific diagnostic tests (Tables 3 and 4).

3.1.3.2.1 Nocturnal penile tumescence and rigidity test

The nocturnal penile tumescence and rigidity assessment should be performed on at least two separate nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for ten or more minutes [86].

3.1.3.2.2 Intracavernous injection test

The intracavernous injection test gives limited information about the vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within ten minutes after the intracavernous injection and lasts for 30 minutes [87]. Overall, the test is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

3.1.3.2.3 Duplex ultrasound of the penis

A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are generally considered normal [88]. Further vascular investigation is unnecessary when a duplex ultrasound (US) examination is normal.

3.1.3.2.4 Arteriography and dynamic infusion cavernosometry or cavernosography

Arteriography and dynamic infusion cavernosometry or cavernosography should be performed only in patients who are being considered for vascular reconstructive surgery [89].

3.1.3.2.5 Psychiatric assessment

Whenever clinically indicated, patients with psychiatric disorders should be referred to a psychiatrist who is particularly interested in sexual health. In younger patients (< 40 years) with long-term primary ED [34], psychiatric assessment may be helpful before any organic assessment is carried out.

3.1.3.2.6 Penile abnormalities

Surgical correction may be needed in patients with ED and penile abnormalities (e.g. hypospadias, congenital curvature, or Peyronie's disease with preserved rigidity).

3.1.3.3 *Patient education - consultation and referrals*

Consultation with the patient should include a discussion of the expectations and needs of both the patient and their sexual partner. It should also review both the patient's and partner's understanding of ED and the results of diagnostic tests, and provide a rational selection of treatment options [90]. Patient and partner education is an essential part of ED management [90, 91].

Table 3: Indications for specific diagnostic tests

Primary ED (not caused by organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative revascularisation surgery or angioplasty.
Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital penile curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or his partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end stage ED, sexual abuse).

Table 4: Specific diagnostic tests

Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan®
Vascular studies - Intracavernous vasoactive drug injection - Penile Dynamic Duplex Ultrasonography - Penile Dynamic Infusion Caverosometry and Caverosography - Internal pudendal arteriography
Neurological studies (e.g., bulbocavernosus reflex latency, nerve conduction studies)
Endocrinological studies
Specialised psychodiagnostic evaluation

3.1.3.4 Recommendations for the diagnostic evaluation of ED

Recommendations	LE	GR
Take a comprehensive medical and sexual history in every patient.	3	B
Use a validated questionnaire related to erectile dysfunction to assess all sexual function domains and the effect of a specific treatment modality.	3	B
Include a physical examination in the initial assessment of men with erectile dysfunction (ED) to identify underlying medical conditions that may be associated with ED.	4	B
Assess routine laboratory tests, including glucose-lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	4	B
Include specific diagnostic tests in the initial evaluation only in the presence of the conditions presented in Table 3.	4	B

3.1.4 Disease management

3.1.4.1 Treatment options

Erectile dysfunction may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors [30]. These factors may be modified either before, or at the same time as, specific therapies are used. Likewise, ED may be associated with concomitant and underlying conditions (such as, endocrine disorders and metabolic disorders - e.g. diabetes - some cardiovascular problems - e.g. hypertension) which should always be well-controlled as the first step of ED treatment [92]. As a rule, ED can be treated successfully with current treatment options, but it cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g. hypogonadism and hyperprolactinaemia) [73, 76], which potentially can be cured with specific treatment. Most men with ED will be treated with therapeutic options that are not cause specific. This results in a structured treatment strategy that depends on efficacy, safety, invasiveness and cost, as well as patient preference [90]. In this context, physician-patient (partner) dialogue is essential throughout the management of ED. The assessment of treatment options must be tailored according to patient and partner satisfaction, QoL factors as well as treatment-related safety and efficacy. A treatment algorithm for ED is shown in Figure 3.

3.1.4.1.1 Lifestyle management of ED with concomitant risk factors

The basic work-up of the patient must identify reversible risk factors for ED. Lifestyle changes and risk factor modification must precede or accompany any pharmacological treatment. Major clinical potential benefits of lifestyle changes may be obtained in men with specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension [30, 93].

3.1.4.1.2 Erectile dysfunction after radical prostatectomy

Use of pro-erectile drugs following RP is important in achieving post-operative erectile function. Several trials have shown higher rates of erectile function recovery after RP in patients receiving any drug (therapeutic or prophylactic) for ED. Early compared with delayed erectile function treatment seems to impact on the natural healing time of potency [48]. Currently available therapeutic armamentarium follows the treatment algorithm for ED which is shown in Figure 3.

The management of post-RP ED has been revolutionised by the advent of phosphodiesterase 5 inhibitors (PDE5Is), with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. It must be emphasised that post-RP, ED patients are poor responders to PDE5Is. However, PDE5Is are considered as the first-line therapy in patients who have undergone nerve-sparing (NS) surgery regardless of the surgical technique used [48, 49]. A number of clinical parameters have been identified as potential predictors of PDE5Is in men undergoing RP. Patient age and quality of NS technique are key factors in preserving post-RP erectile function [48, 49, 52]. The response rate to sildenafil treatment for ED after RP in different trials has ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP [48, 94]. Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa [95]. Daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery [96]. Conversely, a recent prospective, randomised, placebo-controlled study, which assessed the effects of nightly sildenafil citrate therapy during penile rehabilitation using nocturnal penile rigidity in addition to the IIEF-EF, showed no therapeutic benefit for nightly sildenafil when compared to on-demand dosing in determining recovery of erectile function post-prostatectomy [97].

The effectiveness of tadalafil and vardenafil as on-demand treatment has been evaluated in post-RP ED. A large multicentre trial in Europe and the USA has studied tadalafil in patients with ED following bilateral NS surgery. Erectile function was improved in 71% of patients treated with 20 mg tadalafil vs. 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil vs. 26% with placebo [98]. Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study in North America [99]. Following bilateral NSRP, erectile function improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same cohort of patients showed the benefit of vardenafil compared to placebo in terms of intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience [100]. Moreover, a randomised, double-blind, double-dummy trial in men < 68 years of age and normal pre-operative erectile function who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [101]. Tadalafil was most effective for drug-assisted erectile function in men with ED following NSRP, and data suggested a potential role for tadalafil once daily - provided early after surgery - in contributing to the recovery of post-operative erectile function and possibly protecting penile structural changes [101]. Unassisted erectile function was not improved after cessation of active therapy for nine months [101]. Moreover, taking tadalafil once daily significantly shortened time to erectile function recovery versus placebo over the nine month double/blind treatment period. Conversely tadalafil on demand did not [102]. Likewise, tadalafil once daily improved QoL post-operatively, both at double-blind treatment and open label treatment period [103].

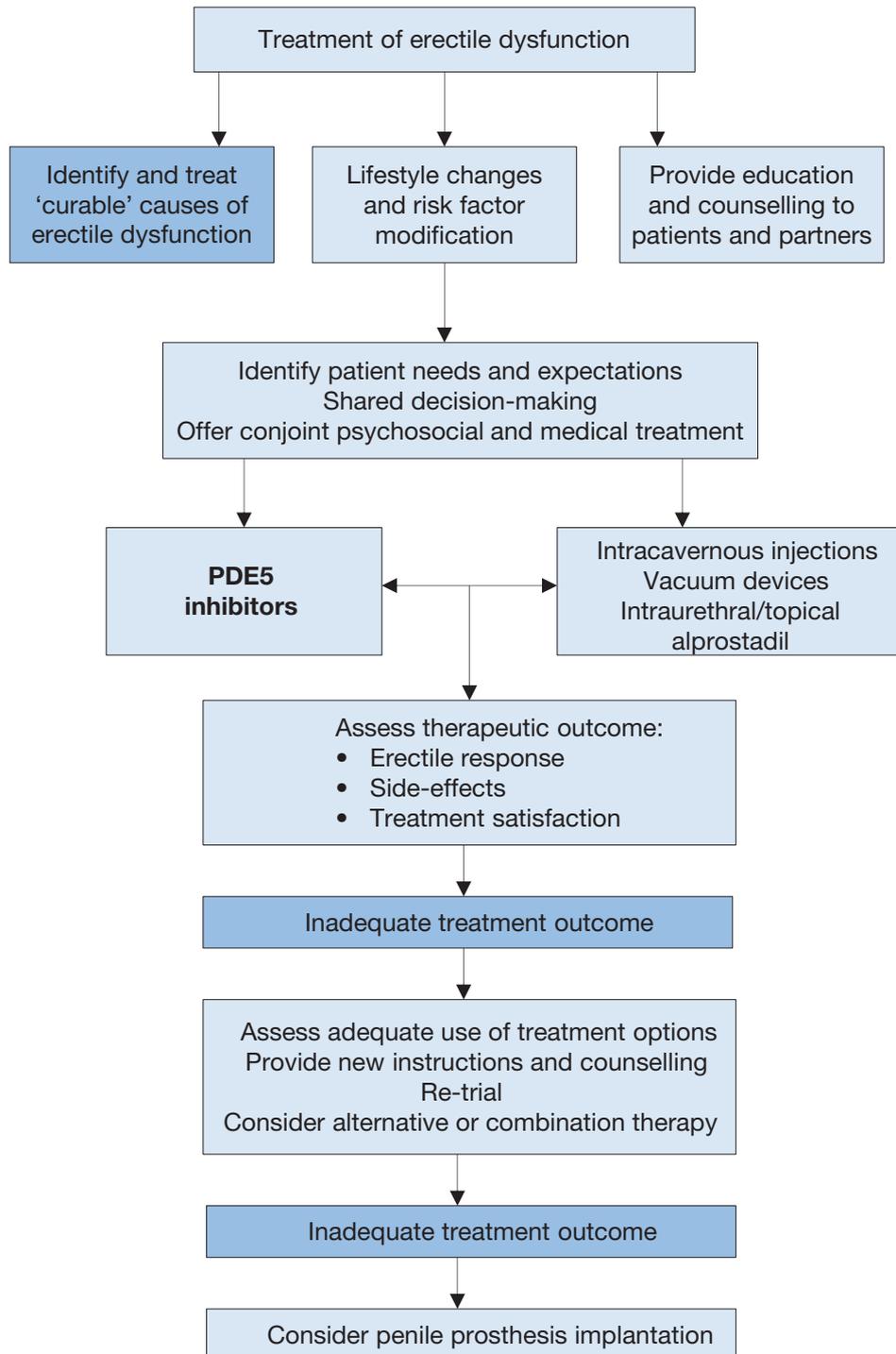
A randomised, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on-demand and nightly dosing of vardenafil in men with ED following bilateral NSRP [104]. In patients whose pre-operative erectile function domain score was > 26, vardenafil was efficacious when used on demand, supporting a paradigm shift towards on-demand dosing with PDE5Is in post-RP ED [104]. A double-blind, placebo-controlled, parallel-group, study in 298 patients with ED after bilateral NSRP randomised to 100 or 200 mg avanafil or placebo (taken 30 minutes before sexual activity) for twelve weeks showed significantly greater increases in sexual encounter profile (SEP) question 2 and SEP3 as well as in mean change of IIEF erectile function domain score with 100 and 200 mg avanafil vs. placebo ($p < 0.01$) [85].

For dosing with avanafil 36.4% (28 of 77) of sexual attempts (SEP3) at fifteen minutes or less were successful vs. 4.5% (2 of 44) for placebo ($p < 0.01$) [105]. A recently conducted meta-analysis confirmed that avanafil had comparable efficacy with sildenafil, vardenafil and tadalafil treatments [106]. Although some authors reported improved erectile function when long-term tadalafil 5 mg once daily is combined with sildenafil as needed [107], more safety analyses are required to recommend such a therapy.

Historically, the treatment options for post-RP ED have included intracavernous injections [108], urethral microsuppository [48, 109], vacuum device therapy [48, 110], and penile implants [48, 111, 112].

Intracavernous injections and penile implants are still suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or contraindicated for post-operative patients (Sections 3.1.4.3 and 3.1.4.4). Recently, the data from a human phase 1 trial with a single intracavernosal injection of autologous adipose-derived regenerative cells (ADRCs) freshly isolated after a liposuction in post-prostatectomy ED patients, showed promising results in restoring normal erectile function with only minor side-effects [113].

Figure 3: Treatment algorithm for erectile dysfunction



3.1.4.1.3 Causes of ED that can be potentially treated with a curative intent

3.1.4.1.3.1 Hormonal causes

The advice of an endocrinologist may be beneficial for managing patients with hormonal abnormalities [76]. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes (e.g. a functional pituitary tumour resulting in hyperprolactinaemia) [76, 114]. When clinically indicated [115], testosterone supplementation (TS) (intramuscular, oral, or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded [35, 73, 116]. Before initiating TS, digital rectal examination (DRE), serum PSA test, haematocrit, liver function tests and lipid profile should be performed [35, 73, 117]. Patients who are given TS should be monitored for clinical response, elevation of haematocrit and development of hepatic or prostatic disorders [35, 73, 117]. Testosterone supplementation is controversial in men with a history of PCa (LE: 4) [118]. Since there is limited evidence suggesting that TS may not pose an undue risk of PCa recurrence or progression, TS is contraindicated in patients with untreated PCa (LE: 4).

Testosterone supplementation is contraindicated in patients with unstable cardiac disease [69, 119]. Conversely, the role of testosterone in the cardiovascular health of men is controversial. Clinical trials examining TS have been insufficiently powered to provide definitive and unequivocal evidence of adverse events in terms of cardiovascular outcomes [120-125]. Current guidelines from the Endocrine Society make no recommendations on whether patients with heart disease should be screened for hypogonadism and do not recommend supplementing testosterone in patients with heart disease to improve survival [72]. However, a recent comprehensive SR and meta-analysis of all placebo-controlled RCTs on the effect of TS on cardiovascular-related problems did not support a causal role between TS and adverse cardiovascular events [119].

3.1.4.1.3.2 Post-traumatic arteriogenic ED in young patients

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate [126]. The lesion must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by dynamic infusion cavernosometry or cavernosography. Vascular surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [126].

3.1.4.1.3.3 Psychosexual counselling and therapy

For patients with a significant psychological problem, psychosexual therapy may be given either alone or with another therapeutic approach in order to improve couple sexual satisfaction and female sexual function [127]. Psychosexual therapy requires ongoing follow-up and has had variable results [128].

3.1.4.2 First-line therapy

3.1.4.2.1 Oral pharmacotherapy

Phosphodiesterase 5 inhibitor hydrolyses cyclic guanosine monophosphate (cGMP) in the cavernosal tissue. Inhibition of PDE5 results in smooth muscle relaxation with increased arterial blood flow, leading to compression of the subtunical venous plexus followed by penile erection [129]. Four potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for the treatment of ED [130]. They are not initiators of erection and require sexual stimulation to facilitate an erection. Efficacy is defined as an erection with rigidity sufficient for penetration.

Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market [131]. It is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and side-effects [131]. Sildenafil is effective from 30-60 minutes after administration [131]. Its efficacy is reduced after a heavy, fatty meal due to delayed absorption. Efficacy may be maintained for up to twelve hours [132]. The pharmacokinetic data of sildenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use [133, 134]. After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% of a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [135]. Sildenafil significantly improved patient scores for IIEF, SEP2, SEP3, and General Assessment Questionnaire (GAQ) and treatment satisfaction. The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established. (LE: 1). Recently, an orally disintegrating tablet (ODT) of sildenafil citrate at the dosage of 50 mg has been developed mainly for the benefit of patients who have difficulty swallowing solid dosage forms.

Tadalafil

Tadalafil was licensed for treatment of ED in February 2003 and is effective from 30 minutes after administration, with peak efficacy after about two hours [136]. Efficacy is maintained for up to 36 hours [136] and is not affected by food. It is administered in on-demand doses of 10 and 20 mg and also an alternative daily dose of 5 mg. The recommended on-demand starting dose is 10 mg and should be adapted according to the patient's response and side-effects [136, 137]. Pharmacokinetic data of tadalafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use. In pre-marketing studies, after twelve weeks of treatment and in a dose-response study, improved erections were reported by 67% and 81% of a general ED population taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the control placebo group [136]. Tadalafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction [136].

Efficacy has been confirmed in post-marketing studies [130, 138]. The efficacy of tadalafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established [139]. Daily tadalafil has also been licensed for the treatment of LUTS secondary to BPH. Therefore, it is useful in patients with concomitant ED and LUTS [140].

Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 minutes after administration [139]. Its effect is reduced by a heavy, fatty meal (> 57% fat). 5, 10 and 20 mg doses have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects [141]. Pharmacokinetic data of vardenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use [141]. After twelve weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of a general ED population taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [141, 142]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies [141, 142]. The efficacy of vardenafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. More recently, an ODT form of vardenafil has been released [142]. Orodispersible tablet formulations offer improved convenience over film-coated formulations and may be preferred by patients. Absorption is unrelated to food intake and they exhibit better bio-availability compared to film-coated tablets [143]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [143-145].

Avanafil

Avanafil is a highly-selective PDE5i that became commercially available in 2013 [146]. Avanafil has a high ratio of inhibiting PDE5 as compared with other PDE subtypes allowing for the drug to be used for ED while minimising adverse effects [147]. 50 mg, 100 mg, and 200 mg doses have been approved for on-demand treatment of ED [146]. The recommended starting dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity and the dosage may be adapted according to efficacy and tolerability [146, 148, 149]. In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58%, and 59% for the 50 mg, 100 mg, and 200 mg avanafil groups, respectively, as compared with approximately 28% for placebo [146, 148]. Data from sexual attempts made within fifteen minutes of dosing showed successful attempts in 64%, 67%, and 71% of cases, with avanafil 50, 100, and 200 mg, respectively. The maximum recommended dosing frequency is once per day. Dosage adjustments are not warranted based on renal function, hepatic function, age or gender [148]. Pharmacokinetic data of avanafil are presented in Table 5 [146, 148]. Adverse events are generally mild in nature (Table 6) [146, 148]. Pairwise meta-analytic data from available studies suggested that avanafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ, with an evident dose-response relationship [146, 150]. Administration with food may delay the onset of effect compared with administration in the fasting state but avanafil can be taken with or without food. The efficacy of avanafil in many groups of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established.

Choice or preference between the different PDE5Is

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for sildenafil, tadalafil, vardenafil, and avanafil. Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, three to four times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it. A recent meta-analysis demonstrated that ED patients who prioritise high efficacy must use sildenafil 50 mg whereas those who optimise tolerability should initiate with tadalafil 10 mg treatment and switch to vardenafil 100 mg if the treatment is not sufficient [138]. Of clinical relevance, vardenafil is not an EMEA or FDA

approved drug. Results of another clinical trial revealed that tadalafil 5 mg once daily may improve the erectile function outcomes among men who had a partial response to on-demand PDE5I therapy [151].

Continuous use of PDE5Is

Animal studies have shown that chronic use of PDE5 inhibitors significantly improves or prevents the intracavernous structure alterations due to age, diabetes, or surgical damage [152-156]. No data exists for a human population. In humans, it has been clinically demonstrated that treatment with tadalafil 5 mg once daily in men complaining of ED of various severities was well tolerated and effective [157]. In 2007, tadalafil 2.5 and 5 mg were approved by the EMA for daily treatment of ED. According to EMA, a once daily regimen with tadalafil 2.5 mg or 5 mg might be considered suitable, based on patient choice and the physician's judgement. In these patients, the recommended dose is 5 mg, taken once a day at approximately the same time. Overall, tadalafil, 5 mg once daily, provides an alternative to on-demand dosing of tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be temporally linked. The appropriateness of the continuous use of a daily regimen should be re-assessed periodically [157, 158]. Continuous dosing may also be used in the comorbid patient with LUTS and ED.

Table 5: Summary of the key pharmacokinetic data for the four PDE5Is currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil 200mg
C _{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T _{max} (median)	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T1/2	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
AUC	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

* Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.

C_{max}: maximal concentration, T_{max}: time-to-maximum plasma concentration; T1/2: plasma elimination half-time; AUC: area under curve or serum concentration time curve.

Table 6: Common adverse events of the four PDE5Is currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	none
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

* Adapted from EMA statements on product characteristics.

Safety issues for PDE5Is

(i) Cardiovascular safety

Clinical trial results for the four PDE5Is and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either RCTs or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5Is had an adverse effect on total exercise time or time-to-ischæmia during exercise testing in men with stable angina. Chronic or on-demand use is well tolerated with a similar safety profile. All PDE5Is are contraindicated in: i) patients who have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia within the last six months; ii) patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg); iii) patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class IV [83, 159-161].

(ii) Nitrates are contraindicated with PDE5Is

Absolute contraindication to PDE5Is is represented by patients who are using any form of organic nitrate (e.g. nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or nitric oxide (NO) donors (e.g. other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate such as “poppers” which is used for recreation). They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used. If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 hours if sildenafil (and probably also vardenafil) is used (half-life, four hours), or at least 48 hours if tadalafil is used (half-life, 17.5 hours), and for no less than twelve hours if avanafil is used (half-life, 6-17 hours) [162].

(iii) Antihypertensive drugs

Co-administration of PDE5Is with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β -blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor [83]. In general, the adverse event profile of a PDE5I is not worsened by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents [163].

 α -Blocker interactions

All PDE5Is show some interaction with α -blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α -blocker (especially doxazosin). Hypotension is more likely to occur within four hours following treatment with an α -blocker. A starting dose of 25 mg is recommended [133].
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his α -blocker therapy. Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension [139, 141, 142].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [136, 164].
- Avanafil labelling currently reports that patients should be stable on α -blocker therapy prior to initiating avanafil. In these patients, avanafil should be initiated at the lowest dose of 50 mg. Conversely, in those patients already taking an optimised dose of avanafil, α -blocker therapy should be initiated at the lowest dose.

Dosage adjustment

Drugs that inhibit the CYP3A4 pathway will inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (e.g. ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin). Therefore, lower doses of PDE5Is are necessary. However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

Management of non-responders to PDE5Is

The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy of the drug. Data suggest that an adequate trial involves at least six attempts with a particular drug [165]. The management of non-responders depends upon identifying the underlying cause. Check that the patient has been using a licensed medication. There is a large counterfeit market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

Check that the medication has been properly prescribed and correctly used. The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The most common causes of incorrect drug use are: i) failure to use adequate sexual stimulation; ii) failure to use an adequate dose; and, iii) failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

PDE5I action is dependent on the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the medication is ineffective. Oral PDE5Is take different times to reach maximal plasma concentrations [132, 134, 143, 150, 166-168]. Although pharmacological activity is achieved at plasma levels well below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all four drugs have an onset of

action in some patients within 15-30 minutes of oral ingestion [134, 143, 150, 166-168], most patients require a longer delay between taking the medication [141, 150, 169, 170]. Absorption of sildenafil can be delayed by a meal, and absorption of vardenafil can be delayed by a fatty meal [171]. Absorption of tadalafil is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse [166]. When avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There is no effect on the extent of exposure (AUC). The small changes in avanafil C_{max} are considered to be of minimal clinical significance [146, 147, 150].

It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about four hours, suggesting that the normal window of efficacy is six to eight hours following drug ingestion, although responses following this time period are well recognised. The half-life of avanafil is six to seventeen hours. Tadalafil has a longer half-life of ~17.5 hours, so the window of efficacy is much longer at ~36 hours. Data from uncontrolled studies suggest patient education can help salvage an apparent non-responder to a PDE5I [172-176]. After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function can be effectively restored following re-administration of the relevant PDE5I [172-174].

Very recently, data suggested that response to sildenafil treatment was also dependent on polymorphism in the PDE5A gene, which encodes the principal cGMP-catalyzing enzyme in the penis, regulating cGMP clearance, and it is the primary target of sildenafil [177]. Overall, the findings of a meta-regression aimed at evaluating the effectiveness and prognostic factors of PDE5I to treat ED showed that PDE5Is are more effective in Caucasians than Asians, and in patients with more severe ED [178].

Clinical strategies in patients correctly using a PDE5Is

There is controversial evidence suggesting that, in patients with testosterone deficiency, TS might improve a patient's response to a PDE5I [73, 179-181]. Modification of other risk factors may also be beneficial as discussed in section 3.1.4.1.1. Limited data suggest that some patients might respond better to one PDE5I than to another [182]. Although these differences might be explained by variations in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5I might be helpful. Moreover, mainly in patients with severe ED, it has been suggested to combine tadalafil daily dosing with short acting PDE5I (such as sildenafil), without any significant increase in terms of side-effects [183]. If drug treatment fails, then patients should be offered an alternative therapy such as intracavernous injection therapy or use of a vacuum erection device (VED).

The combination of long-acting injectable testosterone undecanoate and tadalafil 5 mg once daily produced a significant improvement in terms of EF of combined treatment [184]. Moreover, the improvement in EF was well maintained, even after the cessation of treatment.

3.1.4.2.2 Vacuum erection devices

Vacuum erection devices (VED) provide passive engorgement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora. Published data report that efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% [185, 186]. Most men who discontinue use of VEDs do so within three months. Long-term use of VEDs decreases to 50-64% after two years [187]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in < 30% of patients [186]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes after intercourse. Vacuum erection devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy. Vacuum erection devices may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED [185, 186].

3.1.4.2.3 Shockwave therapy

The use of low-intensity extracorporeal shockwave therapy (LI-SWT) was proposed as a novel treatment for ED [188-192]. In this context, the number of studies of LI-SWT for ED has increased dramatically throughout recent years. Overall, most of these studies reported encouraging results, regardless of variation in LI-SWT set-up parameters or treatment protocols. As a whole these studies suggest that LI-SWT could significantly improve the IIEF and Erection Hardness Score of ED patients [193]. The publication of robust evidence from additional RCTs and longer-term follow-up would provide more confidence regarding use of LI-SWT for ED patients. Therefore clear recommendations cannot be given.

3.1.4.3 Second-line therapy

Patients not responding to oral drugs may be offered intracavernous injections. The success rate is high (85%) [194, 195]. Intracavernous administration of vasoactive drugs was the first medical treatment for ED introduced more than twenty years ago [176, 196].

3.1.4.3.1 Intracavernous injections

3.1.4.3.1.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for intracavernous treatment of ED [176, 196]. Intracavernous alprostadil is most efficacious as monotherapy at a dose of 5-40 µg (of note, 40 µg dose is not registered in every European country). The erection appears after five to fifteen minutes and lasts according to the dose injected. An office-training programme is required for the patient to learn the correct injection process. In cases of limited manual dexterity, the technique may be taught to their partners. The use of an automatic special pen that avoids a view of the needle can resolve fear of penile puncture and simplifies the technique. Efficacy rates for intracavernous alprostadil of > 70% have been found in the general ED populations, as well as in patient subgroups (e.g. diabetes or CVD), with reported sexual activity of 94% after the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners [176, 196]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), prolonged erections (5%), priapism (1%), and fibrosis (2%) [176, 196, 197]. Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia [176, 196, 198]. Cavernosal fibrosis (from a small haematoma) usually clears within a few months after temporary discontinuation of the injection programme. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernous injections indefinitely. Systemic side-effects are uncommon. The most common is mild hypotension, especially when using higher doses. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders. Despite these favourable data, drop-out rates of 41-68% have been described for intracavernous pharmacotherapy [176, 196, 199, 200], with most drop-outs occurring within the first two to three months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year. Reasons for discontinuation included desire for a permanent modality of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up is important in addressing patient withdrawal from an intracavernous injection programme [201].

3.1.4.3.1.2 Combination therapy

Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating side-effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy due to its high incidence of side-effects as monotherapy. Papaverine is currently not licensed for the treatment of ED.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide, usually combined with the main drugs [202, 203]. Most combinations are not standardised and some drugs have limited availability worldwide.
- Papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg), have been widely used with improved efficacy rates, although they have never been licensed for ED [204, 205]. The triple combination regimen of papaverine, phentolamine and alprostadil has the highest efficacy rates, reaching 92%; this combination has similar side-effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose).
- Vasoactive intestinal peptide (VIP) (25 µg) plus phentolamine mesylate (1-2 mg) (Invicorp™, currently licensed in Scandinavia), is a combination of two active components with complementary modes of action. Clinical studies showed that the combination is an effective treatment for intracavernous injections in > 80% of men with ED, including those who have failed to respond to other therapies and, unlike existing intracavernous therapies, is associated with a very low incidence of penile pain and virtually negligible risk of priapism [206].

Despite high efficacy rates, 5-10% of patients do not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone [207]. However, combination therapy is associated with an increased incidence of adverse effects in 33% of patients, including dizziness in 20% of patients. This strategy can be considered in carefully selected patients before proceeding to a penile implant (LE: 4).

3.1.4.3.1.3 Intraurethral/topical alprostadil

A specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) has been approved as a treatment for ED [208]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, only the higher doses (500 and 1,000 µg) have been used with low consistency response rates [208-210]. The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy [209, 210].

The most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are very rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration. Efficacy rates are significantly lower than intracavernous pharmacotherapy [195]. Intraurethral pharmacotherapy is a second-line therapy and provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

Topical alprostadil is another way of administering alprostadil. It is a cream that includes a permeation enhancer in order to facilitate absorption of alprostadil (200 and 300µg) through the urethral meatus [211]. Clinical data are limited. Significant improvement compared to placebo was recorded for IIEF, SEP2 and SEP3 in a broad range of patients with mild-to-severe ED [212]. Side-effects include penile erythema, penile burning and pain. Systemic side-effects are very rare. Topical alprostadil is approved and it is only available in some European countries.

3.1.4.4 Third-line therapy (penile prostheses)

The surgical implantation of a penile prosthesis may be considered in patients who do not respond to pharmacotherapy or who prefer a permanent solution to their problem [213]. The two currently available classes of penile implants include inflatable (2- and 3-piece) and malleable devices [48, 111, 214, 215]. Most patients prefer the 3-piece inflatable devices due to the more “natural” erections obtained. Likewise, 3-piece inflatable devices provide the best rigidity and the best flaccidity because they will fill every part of the corporal bodies. However, the 2-piece inflatable prosthesis can be a viable option among patients who are deemed at high-risk of complications with reservoir placements. Malleable prostheses result in a firm penis, which may be manually placed in an erect or flaccid state [48, 111, 214, 215].

There are two main surgical approaches for penile prosthesis implantation: penoscrotal and infrapubic [214-217]. The penoscrotal approach provides an excellent exposure, it affords proximal crural exposure if necessary, avoids dorsal nerve injury and permits direct visualisation of pump placement. However, with this approach, the reservoir is blindly placed into the retropubic space, which can be a problem in patients with a history of major pelvic surgery (mainly radical cystectomy). The infrapubic approach has the advantage of reservoir placement under direct vision, but the implantation of the pump may be more challenging, and patients are at a slightly increased risk of penile dorsal nerve injury. Revision surgery is associated with decreased outcomes and may be more challenging. Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED based on appropriate consultation [48, 111, 214, 218-224]. In patients with favourable oncologic prognosis after RP for PCa, combination surgery for treatment of ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established, definitive role to address this problem [48, 111, 225-227]. A structured psychosexual counselling may improve sexual activities and erotic functions in both patients and their partners after penile implants [228].

3.1.4.4.1 Complications

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used 3-piece prosthesis (AMS 700CX/CXR™ and Coloplast Alpha ITM) resulted in mechanical failure rates of < 5% after five years of follow-up [111, 229, 230]. Careful surgical techniques with proper antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduces infection rates to 2-3% with primary implantation in low-risk patients and in high volume centres [231-233]. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [111, 231, 234-237]. Higher-risk populations include patients undergoing revision surgery, those with impaired host defenses

(immunosuppression, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis [17, 111, 214, 233, 238, 239]. Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement with a new prosthesis has been described using a washout protocol with successful salvages achieved in > 80% of cases [232, 233, 238]. The majority of revisions are secondary to mechanical failure and combined erosion or infection [236, 240]. 93% of cases are successfully revised, providing functioning penile prosthesis [231-233, 241, 242].

3.1.4.4.2 Conclusions third-line therapy

Penile implants are an attractive solution for patients who do not respond to more conservative therapies. There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rates.

3.1.4.5 Recommendations for the treatment of ED

Recommendations	LE	GR
Enact lifestyle changes and risk factor modification prior to or accompanying erectile dysfunction (ED) treatment.	1a	A
Start pro-erectile treatments at the earliest opportunity after radical prostatectomy.	1b	A
Treat a curable cause of ED first, when found.	1b	B
Use phosphodiesterase type 5 inhibitors (PDE5Is) as first-line therapy.	1a	A
Assess all patients for inadequate/incorrect prescriptions and poor patient education, since they are the main causes of a lack of response to PDE5Is.	3	B
Use vacuum erection devices as a first-line therapy in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED.	4	C
Use intracavernous injections as second-line therapy.	1b	B
Use implantation of a penile prosthesis as third-line therapy.	4	C

3.1.4.6 Follow-up

Follow-up is important in order to assess efficacy and safety of the treatment provided. It is also essential to assess patient satisfaction since successful treatment for ED goes beyond efficacy and safety. Physicians must be aware that there is no single treatment that fits all patients or all situations as described in detail in the previous section.

3.2 Premature ejaculation

3.2.1 Epidemiology/aetiology/pathophysiology

Although premature ejaculation (PE) is a common male sexual dysfunction, it is poorly understood. Patients are often unwilling to discuss their symptoms and many physicians do not know about effective treatments. As a result, patients may be misdiagnosed or mistreated [2].

3.2.1.1 Epidemiology

The major problem in assessing the prevalence of PE is the lack of an accurate (validated) definition at the time the surveys were conducted [243]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the USA National Health and Social Life Survey (NHSLs) study [244]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that the PE prevalence is as high as 20-30% based on the relatively low number of men who present for treatment of PE. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower [245]. According to the four PE subtypes proposed by Waldinger *et al.* [246], the prevalence rates were 2.3% (lifelong PE), 3.9% (acquired PE), 8.5% (natural variable PE) and 5.1% (premature-like ejaculatory dysfunction) [247]. An approximately 5% prevalence of acquired PE and lifelong PE in general populations is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency of less than 2 minutes [248].

3.2.1.2 Pathophysiology and risk factors

The aetiology of PE is unknown, with little data to support suggested biological and psychological hypotheses, including anxiety, penile hypersensitivity, and 5-HT receptor dysfunction [249]. In addition, the pathophysiology of PE is largely unknown. All the physiological events leading up to the forceful expulsion of sperm at the urethral meatus are not impaired in PE patients. A significant proportion of men with ED also experience PE

[250, 251]. High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED. According to the NHSLs, the prevalence of PE is not affected by age [244, 245], unlike ED, which increases with age. PE is not affected by marital or income status [244]. However, PE is more common in Black men, Hispanic men and men from Islamic backgrounds [252, 253] and may be higher in men with a lower educational level [244, 250]. Other risk factors may include a genetic pre-disposition [254], poor overall health status and obesity [244], prostate inflammation [255-257], thyroid hormone disorders [258], diabetes [259], emotional problems and stress [244, 260], and traumatic sexual experiences [244, 250]. In the only published study on risk modification/prevention strategies [261], successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in intravaginal ejaculatory latency time (IELT) and ejaculatory control compared to untreated patients [262].

3.2.1.3 *Impact of PE on QoL*

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less frequent intercourse [263, 264]. However, the negative impact of PE extends beyond sexual dysfunction. Premature ejaculation can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [263, 265]. Sex drive and overall interest in sex does not appear to be affected by PE [266]. However, the partner's satisfaction with the sexual relationship decreases with increasing severity of the man's condition [267]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment. In the Global Study of Sexual Attitudes and Behaviors survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems [250], with men more likely to seek treatment for ED than for PE [250]. In the Premature Ejaculation Prevalence and Attitudes survey, only 9% of men with self-reported PE consulted a doctor [245]. The main reasons for not discussing PE with their physician are embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE [268, 269]. Physicians need to encourage their patients to talk about PE.

3.2.2 **Classification**

There have previously been two official definitions of PE, neither of which have been universally accepted:

In the Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision (DSM-IV-TR), PE is defined as a '*persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity*' [270]. This DSM definition has been recently updated in the DSM V edition [271].

The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of PE which is the first evidence-based definition [272]. Premature ejaculation (lifelong and acquired) is a male sexual dysfunction characterised by the following:

1. Ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired PE).
2. The inability to delay ejaculation on all or nearly all vaginal penetrations.
3. Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

Two more PE syndromes have been proposed [273]:

- 'Variable PE' is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Subjective PE' is characterised by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology.

The addition of these new types may aid patient stratification, diagnosis and treatment, but their exact role remains to be defined [274].

3.2.3 **Diagnostic evaluation**

Diagnosis of PE is based on the patient's medical and sexual history [275, 276]. History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual

stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED. Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection [251, 277]. Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE [278]. There are several overlapping definitions of PE, with four shared factors (Table 7), resulting in a multidimensional diagnosis [279].

Table 7: Common factors in different definitions of PE

Time to ejaculation assessed by IELT
Perceived control
Distress
Interpersonal difficulty related to the ejaculatory dysfunction

3.2.3.1 *Intravaginal ejaculatory latency time*

The use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [280, 281]. Intravaginal ejaculatory latency time has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse [282]. In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation). In everyday clinical practice, self-estimated IELT is sufficient [283]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [284]. Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) on control over ejaculation and satisfaction with sexual intercourse (scale ranging from 0 = very poor to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all, to 4 = extremely). However, self-estimated IELT may be over-estimated by approximately one minute and therefore it must be carefully substituted with stopwatch-measured IELT while identifying men with the complaint of lifelong PE in a clinical setting [285]. Stopwatch-measured IELT is necessary in clinical trials. While IELT is an objective tool for PE assessment, a recent study reported that sexual satisfaction and distress correlated more strongly with the feeling of control than with the self-reported latency time [286].

3.2.3.2 *PE assessment questionnaires*

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs [279]. Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): five-item questionnaire based on focus groups and interviews from the USA, Germany and Spain. Assesses control, frequency, minimal stimulation, distress and interpersonal difficulty [287, 288]. A total score > 11 suggests a diagnosis of PE, a score of 9 or 10 suggests a probable diagnosis of PE while a score of < 8 indicates a low likelihood of PE.
- Arabic Index of Premature Ejaculation (AIPE): seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction for the patient and partner, anxiety or depression [289]. A cut-off score of 30 (range of scores 7-35) discriminated best PE diagnosis. Severity of PE was classified as severe (score: 7-13), moderate (score: 14-19), mild-to-moderate (score: 20-25) and mild (score: 26-30).

The most widely used tool is the PEDT. However, there is a low correlation between a diagnosis provided by PEDT and a self-reported diagnosis. A recent study reported that only 40% of men with PEDT-diagnosed PE and 19% of men with probable PE self-reported the condition [290]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [291]. Other questionnaires used to characterise PE and determine treatment effects include the PEP [281], Index of Premature Ejaculation (IPE) [292] and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EJD) [293]. Currently, their role is optional in everyday clinical practice.

3.2.3.3 *Physical examination and investigations*

Physical examination may be part of the initial assessment of men with PE. It may include a brief examination of the endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as endocrinopathy, Peyronie's disease, urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended [275].

3.2.3.4 Recommendations for the diagnostic evaluation of PE

Recommendations	LE	GR
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	1a	A
Do not use stopwatch-measured IELT in clinical practice.	2a	B
Do not use patient-reported outcomes in clinical practice.	3	C
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	3	C
Do not perform routine laboratory or neurophysiological tests. They should only be directed by specific findings from history or physical examination.	3	C

3.2.4 Disease management

In men for whom PE causes few, if any, problems, treatment is limited to psychosexual counselling and education. Before beginning treatment, it is essential to discuss the patient's expectations thoroughly. Furthermore, it is important firstly to treat, if present, ED and possibly prostatitis. Various behavioural techniques have been beneficial in treating PE and are indicated for patients uncomfortable with pharmacological therapy. In lifelong PE, behavioural techniques are not recommended for first-line treatment. They are time-intensive, require the support of a partner and can be difficult to perform. In addition, long-term outcomes of behavioural techniques for PE are unknown. Pharmacotherapy is the basis of treatment in lifelong PE. Dapoxetine is the only on-demand pharmacological treatment approved for PE in many countries except for the USA. All other medications used in PE are off-label indications. Chronic antidepressants including selective serotonin re-uptake inhibitors (SSRIs) and clomipramine, a tricyclic antidepressant and on-demand topical anaesthetic agents have consistently shown efficacy in PE. Long-term outcomes for pharmacological treatments are unknown. An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grades of recommendation are provided and a treatment algorithm is presented (Figure 4).

3.2.4.1 Psychological/behavioural strategies

Behavioural strategies mainly include the 'stop-start' programme developed by Semans [294] and its modification, the 'squeeze' technique, proposed by Masters and Johnson [295]:

- In the 'stop-start' programme, the partner stimulates the penis until the patient feels the urge to ejaculate. At this point, he instructs his partner to stop, waits for the sensation to pass and then stimulation is resumed.
- The 'squeeze' technique is similar but the partner applies manual pressure to the glans just before ejaculation until the patient loses his urge.

Both these procedures are typically applied in a cycle of three pauses before proceeding to orgasm. Behavioural strategies are based on the hypothesis that PE occurs because the man fails to appreciate the sensations of heightened arousal and to recognise the feelings of ejaculatory inevitability. Re-training may attenuate stimulus-response connections by gradually exposing the patient to progressively more intense and more prolonged stimulation, while maintaining the intensity and duration of the stimulus just below the threshold for triggering the response. There are several modifications of these techniques making comparison difficult.

Masturbation before anticipation of sexual intercourse is a technique used by younger men. Following masturbation, the penis is desensitised resulting in greater ejaculatory delay after the refractory period is over. In a different approach, the man learns to recognise the signs of increased sexual arousal and how to keep his level of sexual excitement below the intensity that elicits the ejaculatory reflex. Efficacy is similar to the 'stop-start' programme [296].

Psychological factors may be associated with PE and should be addressed in treatment. These factors mainly relate to anxiety, but could also include relationship factors [264]. The limited studies available suggest that behavioural therapy, as well as functional sexological treatment, lead to improvement in the duration of intercourse and sexual satisfaction [297, 298].

Overall, short-term success rates of 50-60% have been reported [297, 298], with limited evidence on the efficacy of these behavioural therapies on IELT improvement [299]. A double-blind, randomised, crossover

study showed that pharmacological treatment (chlomipramine, sertraline, paroxetine and sildenafil) resulted in greater IELT prolongation than behavioural therapy [300]. Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long-term [301, 302]. Behavioural therapy may be most effective when used to 'add value' to medical interventions. Combination of dapoxetine and behavioural treatment was more effective than dapoxetine alone in patients with lifelong PE in a prospective, randomised trial [303]. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

3.2.4.2 Pharmacotherapy

3.2.4.2.1 Dapoxetine

Dapoxetine hydrochloride is a short-acting SSRI, with a pharmacokinetic profile suitable for on-demand treatment for PE. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [304]. Dapoxetine has been investigated in 6,081 subjects to date [305]. It is approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA. Both available doses of dapoxetine (30 mg and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold in patients with baseline average IELT < 0.5 minutes [306, 307]. In RCTs, dapoxetine, 30 mg or 60 mg one to two hours before intercourse, was effective from the first dose on IELT and increased ejaculatory control, decreased distress, and increased satisfaction. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [307-309]. Treatment-related side-effects were dose-dependent and included nausea, diarrhoea, headache and dizziness. Side-effects were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [283]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [310]. Moreover, dapoxetine is found to be safer compared with other anti-depressants which are used for the treatment of PE [311].

Regarding a combination of PDE5Is with dapoxetine, the addition of dapoxetine to a given regimen of PDE5Is may increase the risk of possible prodromal symptoms that may progress to syncope compared to both PDE5Is inhibitors and SSRIs administered alone. Generally, when dapoxetine is co-administered with PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [312]. A low rate of vasovagal syncope was reported in phase 3 studies. According to the summary of product characteristics, orthostatic vital signs (blood pressure and heart rate) must be measured prior to starting dapoxetine. No cases of syncope were observed in a post-marketing observational study, which had identified patients at risk for orthostatic reaction using the patient's medical history and orthostatic testing [313].

The mechanism of action of short-acting SSRIs in PE is still speculative. Dapoxetine resembles the antidepressant SSRIs in the following ways: the drug binds specifically to the 5-HT re-uptake transporter at subnanomolar levels, has only a limited affinity for 5-HT receptors and is a weak antagonist of the 1A-adrenoceptors, dopamine D1 and 5-HT2B receptors. The rapid absorption of dapoxetine might lead to an abrupt increase in extracellular 5-HT following administration that might be sufficient to overwhelm the compensating autoregulation processes. Does the mechanism of action of short-acting SSRIs differ from that of the conventional chronic SSRI mechanism of action? Either such agents do not cause the auto-receptor activation and compensation reported using chronic SSRIs, or these effects occur, but they simply cannot prevent the action of short-acting SSRIs [314].

3.2.4.2.2 Off-label use of antidepressants: SSRIs and clomipramine

Ejaculation is commanded by a spinal ejaculation generator [315, 316] under excitatory or inhibitory influences from the brain and the periphery [259]. 5-hydroxytryptamine (5-HT or serotonin) is involved in ejaculatory control, with its ejaculation-retarding effects likely to be attributable to activation of 5-HT1B and 5-HT2C receptors, both spinally and supraspinally. By contrast, stimulation of 5-HT1A receptors precipitates ejaculation [314].

Selective serotonin re-uptake inhibitors are used to treat mood disorders, but can delay ejaculation and are therefore widely used 'off-label' for PE. As for depression, SSRIs must be given for one to two weeks to be effective in PE [314]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT1A and 5-HT1B receptors [317]. Clomipramine, the most serotonergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment [318]. Selective serotonin re-uptake inhibitors have revolutionised treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 [319]. Before dapoxetine, daily treatment with SSRIs was the first choice of treatment in PE. Commonly used SSRIs include citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar pharmacological mechanism of action.

Several SRs and meta-analyses of all drug treatment studies reported that, despite methodological problems in most studies, there still remained several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE [320, 321]. Nevertheless, despite significant increase in IELT, there are no data available concerning the PROs in PE patients treated with daily SSRIs. Based on this meta-analysis, SSRIs were expected to increase the geometric mean IELT by 2.6-fold to 13.2-fold. Paroxetine was found to be superior to fluoxetine, clomipramine and sertraline. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg; there was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective [322, 323].

Ejaculation delay may start a few days after drug intake, but it is more evident after one to two weeks since receptor de-sensitisation requires time to occur. Although efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after six to twelve months [318]. Common side-effects of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration; which are usually mild and gradually improve after two to three weeks [274, 306]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of a theoretical risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents with PE aged eighteen years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily dosed SSRIs which may be associated with a SSRI withdrawal syndrome [283].

In one controlled trial, on-demand use of clomipramine (but not paroxetine), three to five hours before intercourse, was reported to be efficacious, though IELT improvement was inferior compared to daily treatment with the same drug [324]. However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects [325, 326]. Individual countries' regulatory authorities strongly advise against prescribing medication for indications if the medication in question is not licensed/approved and prescription of off-label medication may present difficulties for physicians.

3.2.4.2.3 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [327]. Several trials [328, 329] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation. A recent meta-analysis confirmed the efficacy and safety of these agents for the treatment of PE [330].

3.2.4.2.3.1 Lidocaine-prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream increased the IELT from one minute in the placebo group to 6.7 minutes in the treatment group [331]. In another randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream significantly increased the stop-watch-measured IELT from 1.49 to 8.45 minutes while no difference was recorded in the placebo group (1.67 to 1.95 minutes) [332]. Lidocaine-prilocaine cream (5%) is applied for 20-30 minutes prior to intercourse. Prolonged application of topical anaesthetic (30-45 minutes) may result in loss of erection due to numbness of the penis in a significant percentage of men [331]. A condom will prevent diffusion of the topical anaesthetic agent into the vaginal wall causing numbness in the partner.

Alternatively, the condom may be removed prior to sexual intercourse and the penis washed clean of any residual active compound. Although no significant side-effects have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product.

An experimental aerosol formulation of lidocaine, 7.5 mg, plus prilocaine, 2.5 mg (Topical Eutectic Mixture for Premature Ejaculation [TEMPE]), was applied five minutes before sexual intercourse in 539 males. There was an increase in the geometric mean IELT from a baseline of 0.58 minutes to 3.17 minutes during three months of double-blind treatment; a 3.3-fold delay in ejaculation compared with placebo ($p < 0.001$) [333].

3.2.4.2.3.2 Tramadol

Tramadol is a centrally acting analgesic agent that combines opioid receptor activation and re-uptake inhibition

of serotonin and noradrenaline. Tramadol is readily absorbed after oral administration and has an elimination half-life of five to seven hours. For analgesic purposes, tramadol can be administered between three and four times daily in tablets of 50-100 mg. Side-effects were reported at doses used for analgesic purposes (up to 400 mg daily) and include constipation, sedation and dry mouth. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [334]. This mechanism of action distinguishes tramadol from other opioids, including morphine. However, in May 2009, the US Food and Drug Administration released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [335].

A large, randomised, double-blind, placebo-controlled, multi-centre twelve week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by ODT in the treatment of PE [336]. A bioequivalence study had previously been performed that demonstrated equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT < 2 minutes, increases in the median IELT of 0.6 minutes (1.6-fold), 1.2 minutes (2.4-fold) and 1.5 minutes (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose-response effect with tramadol. The tolerability during the twelve-week study period was acceptable. Several other studies also reported that tramadol exhibits a significant dose-related efficacy and side-effects over placebo for treatment of PE [337]. Moreover, the efficacy and safety of tramadol have been confirmed in SRs and meta-analyses [338, 339].

Tramadol has shown a moderate beneficial effect with a similar efficacy as dapoxetine. From what is known about the neuropharmacology of ejaculation and the mechanism of action of tramadol, the delaying effect on ejaculation could be explained by combined CNS μ -opioid receptor stimulation and increased brain 5-HT availability. However, efficacy and tolerability of tramadol would have to be confirmed in more patients and longer-term.

3.2.4.2.4 Other drugs

3.2.4.2.4.1 Phosphodiesterase type 5 inhibitors

There is only one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo [340]. Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and decreased the refractory time to achieve a second erection after ejaculation.

Several open-label studies showed that PDE5Is combined with an SSRI is superior to SSRI monotherapy:

- Sildenafil combined with paroxetine improved IELT significantly and satisfaction vs. paroxetine alone [341];
- Sildenafil combined with sertraline improved IELT and satisfaction significantly vs. sertraline alone [342];
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [343];
- Tadalafil combined with paroxetine significantly improved IELT and satisfaction vs. paroxetine and tadalafil alone [344];
- Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction vs. behavioural therapy alone [345].

There are very limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [346, 347]. However, recent meta-analyses demonstrated that the combined use of SSRIs and PDE5Is may be more effective compared with SSRIs or PDE5Is monotherapy [348-350].

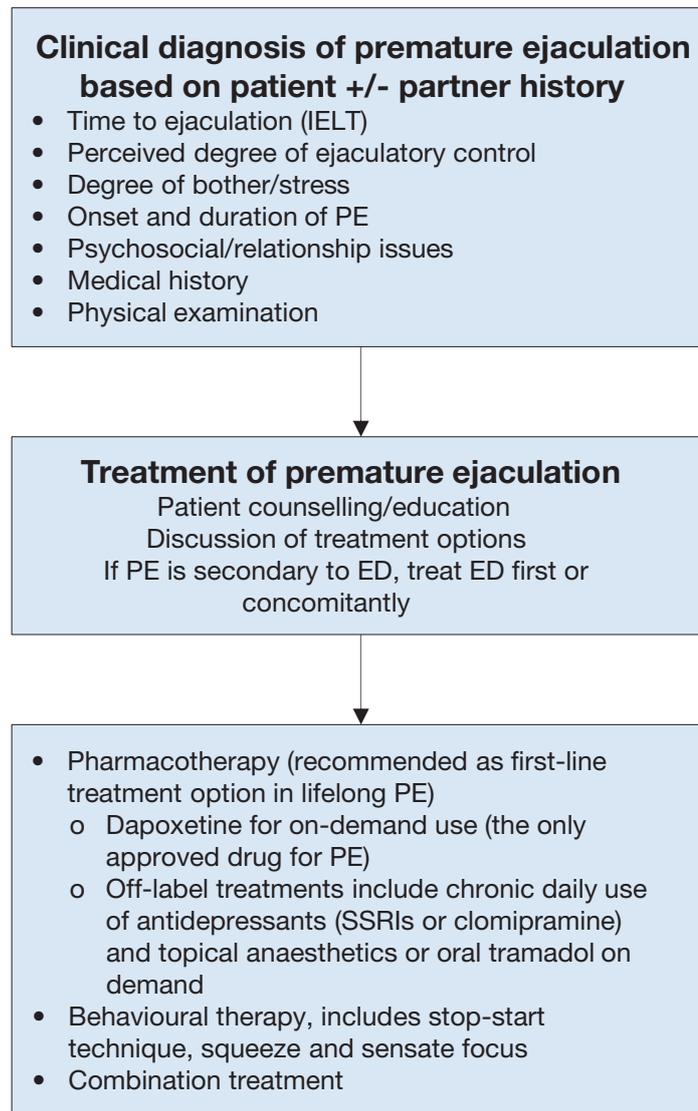
3.2.4.3 Summary of evidence on the epidemiology/aetiology/pathophysiology of PE

Summary of evidence	LE
Pharmacotherapy includes either dapoxetine on demand (a short-acting SSRI that is the only approved pharmacological treatment for premature ejaculation) or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing. With all antidepressant treatment for premature ejaculation, recurrence is likely after treatment cessation.	1a

3.2.4.4 Recommendations for the treatment of PE

Recommendations	LE	GR
Treat erectile dysfunction, other sexual dysfunction or genitourinary infection (e.g. prostatitis first).	2a	B
Use pharmacotherapy as first-line treatment of lifelong premature ejaculation (PE).	1a	A
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRI's).	1b	A
Use tramadol on demand as a weak alternative to SSRI's.	2a	B
Do not use PDE5Is in patients with premature ejaculation without erectile dysfunction.	3	C
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	3	C

Figure 4: Management of Premature Ejaculation*



* Adapted from Lue *et al.* 2004 [351].

ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

3.3 Penile curvature

3.3.1 Congenital penile curvature

3.3.1.1 Epidemiology/aetiology/pathophysiology

Congenital curvature is rare. One well-performed study reports an incidence of less than 1% [352] while there

are reports from quality studies which claim that it is more common with prevalence rates of 4-10% in the absence of hypospadias [353].

Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of cases the curvature is ventral but it can also be lateral and rarely dorsal.

3.3.1.2 *Diagnostic evaluation*

Taking a medical and sexual history is usually sufficient to establish the diagnosis of congenital penile curvature. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and severe curvature can make intercourse difficult or impossible. Physical examination during erection (autophotograph or after intracavernous injection of vasoactive drugs) is useful to document curvature and exclude other pathologies [354].

3.3.1.3 *Disease management*

The treatment of this disorder is surgical correction deferred until after puberty. Results from a recent survey suggest that men with possible untreated ventral penile curvature reported more dissatisfaction with penile appearance, increased difficulty with intercourse, and more unhealthy mental days therefore supporting correction of congenital penile curvature in childhood [355]. Surgical treatments for congenital penile curvature generally share the same principles as in Peyronie's disease (presented in detail in the next section). Nesbit procedure with excision of an ellipse of the tunica albuginea is the gold standard of treatment but many other techniques have been described and employed. Plication techniques are widely used including techniques producing a de-rotation of the corporal bodies [356]. A new modification of the latter technique has been suggested; Shaeer's corporal rotation enables correction of ventral congenital penile curvature, with minimal narrowing and shortening [357]. Most of the time, dissection of the dorsal neurovascular bundle is required in order to avoid loss of sensation and ischaemic lesions in the glans penis [358-360].

3.3.1.4 *Summary of evidence and recommendation for congenital penile curvature*

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Physical examination during erection is useful for documentation of the curvature and exclusion of other pathologies.	3
Surgery is the only treatment option which is deferred until after puberty and can be performed at any time in adult life.	3

Recommendation	LE	GR
Use Nesbit and other plication techniques for the treatment of congenital penile curvature in patients who undergo surgery.	3	B

3.3.2 *Peyronie's Disease*

3.3.2.1 *Epidemiology/aetiology/pathophysiology*

3.3.2.1.1 *Epidemiology*

Epidemiological data on Peyronie's disease (PD) are limited. Prevalence rates of 0.4-9% have been published, with a higher prevalence in patients with ED and diabetes [361-368]. A recent, well conducted survey indicates that the prevalence of definitive and probable cases of PD in the US is 0.7% and 11%, respectively, suggesting that PD is an under-diagnosed problem [369]. The typical age of a patient with PD is 55-60 years.

3.3.2.1.2 *Aetiology*

The aetiology of PD is unknown. However, an insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology of the disease [370]. A prolonged inflammatory response will result in the remodelling of connective tissue into a fibrotic plaque [370-372]. Penile plaque formation can result in curvature which, if severe, may prevent penetrative sexual intercourse.

3.3.2.1.3 *Risk factors*

The most commonly associated comorbidities and risk factors are diabetes, hypertension, lipid abnormalities, ischaemic cardiopathy, ED, smoking, and excessive consumption of alcohol [364, 368, 373, 374]. Dupuytren's contracture is more common in patients with PD affecting 9-39% of patients [365, 375-377] while 4% of patients with Dupuytren's contracture reported Peyronie's disease [376].

3.3.2.1.4 Pathophysiology

Two phases of the disease can be distinguished [378]. The first is the acute inflammatory phase, which may be associated with pain in the flaccid state or painful erections and a palpable nodule or plaque in the tunica of the penis; typically a penile curvature begins to develop. The second is the fibrotic phase (chronic phase) with the formation of hard palpable plaques that can be calcified, which also results in disease stabilisation and no further progressive curvature. With time, penile curvature is expected to worsen in 30-50% of patients or stabilise in 47-67% of patients, while spontaneous improvement has been reported by only 3-13% of patients [373, 379, 380]. Pain is present in 35-45% of patients during the early stages of the disease [381]. Pain tends to resolve with time in 90% of men, usually during the first twelve months after the onset of the disease [379, 380].

In addition to the physiological and functional alteration of the penis, affected men also suffer significant distress. Validated mental health questionnaires have shown that 48% of men with Peyronie's disease have mild or moderate depression, sufficient to warrant medical evaluation [382].

3.3.2.1.5 Summary of evidence on Peyronie's disease

Summary of evidence	LE
Peyronie's disease is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity.	2b
The contribution of associated comorbidities or risk factors (e.g. diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of Peyronie's disease is still unclear.	3
Two phases of the disease can be distinguished. The first phase is the acute inflammatory phase (painful erections, 'soft' nodule/plaque), and the second phase is the fibrotic/calcifying phase with formation of hard palpable plaques (disease stabilisation).	2b
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (30-50%) or stabilisation (47-67%). Pain is usually present during the early stages of the disease but tends to resolve with time in 90% of men.	2a

3.3.2.2 Diagnostic evaluation

The aim of the initial evaluation is to provide information on the presenting symptoms and their duration (erectile pain, palpable nodules, curvature, length, rigidity, and girth) and erectile function status. It is mandatory to obtain information on the distress provoked by the symptoms and the potential risk factors for ED and Peyronie's disease. A disease-specific questionnaire (Peyronie's disease questionnaire (PDQ)) has been designed to collect data, and it has been validated for use in clinical practice [383]. Also, the utility of the PDQ for monitoring PD-specific psychosexual symptom severity, progression, and treatment response, both clinically and in trials of men with PD has been reported [384].

Major attention should be given to whether the disease is still active, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have an active disease are those with a short symptom duration, pain during erection, or a recent change in penile curvature. Resolution of pain and stability of the curvature for at least three months are well-accepted criteria of disease stabilisation and patients' referral for surgical intervention when indicated [379].

The examination should start with a routine genitourinary assessment, which is then extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia [380]. Penile examination is performed to assess the presence of a palpable node or plaque. There is no correlation between plaque size and the degree of curvature [385]. Measurement of penile length during erection is important because it may have impact on the subsequent treatment decisions [386].

An objective assessment of penile curvature with an erection is mandatory. This can be obtained by a home (self) photograph of a natural erection (preferably) or using a vacuum-assisted erection test or an intracavernous injection using vasoactive agents [387]. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in PD patients [65]. Erectile dysfunction is common in patients with PD (> 50%) but it is important to define whether it pre- or post-dates the onset of Peyronie's disease. It is mainly due to penile vascular disease [373], [385]. The presence of ED and psychological factors may impact on the treatment strategy [388].

Ultrasound measurement of the plaque's size is inaccurate and it is not recommended in everyday clinical practice [389]. Doppler US may be required for the assessment of vascular parameters [388].

3.3.2.2.1 Summary of evidence and recommendations for the diagnosis of Peyronie's disease

Summary of evidence	LE
Ultrasound (US) measurement of the plaque's size is inaccurate and operator dependent.	3
Doppler US is required to ascertain vascular parameters associated with ED.	2a

Recommendations	LE	GR
In the medical and sexual history of patients with Peyronie's disease, include duration of the disease, penile pain, change of penile deformity, difficulty in vaginal intromission due to deformity, and erectile dysfunction.	2b	B
In the physical examination, include assessment of palpable plaques, penile length, extent of curvature (self-photograph, vacuum-assisted erection test or pharmacological-induced erection) and any other possibly related diseases (Dupuytren's contracture, Ledderhose disease).	2a	B
Do not use Peyronie's disease specific questionnaire in everyday clinical practice.	2a	B
Do not use ultrasound (US) measurement of plaque size in everyday clinical practice.	3	C
Use Doppler US only in the case of diagnostic evaluation of erectile dysfunction, to ascertain vascular parameters associated with erectile dysfunction.	2a	B

3.3.2.3 Disease management

3.3.2.3.1 Non-operative treatment

Conservative treatment of Peyronie's disease is primarily focused on patients in the early stage of the disease [380, 390]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy and other topical treatments (Table 8). Shockwave treatment of calcified plaques and clostridial collagenase (CCH) injection in patients with densely fibrotic or calcified plaques have also been suggested [378, 391]. Clostridium collagenase is the only drug approved for the treatment of PD by the FDA. No single drug has been approved by the EMA for the treatment of PD at this time. The results of the studies on conservative treatment for PD are often contradictory making it difficult to provide recommendations in the everyday, real-life setting. This is due to several methodological problems including uncontrolled studies, limited number of patients treated, short-term follow-up and different outcome measures [391]. Moreover, the efficacy of conservative treatment in distinct patient populations in terms of early (inflammatory) or late (fibrotic) phases of the disease is not yet available.

Table 8: Non-operative treatments for Peyronie's disease

Oral treatments
Vitamin E
Potassium para-aminobenzoate (Potaba)
Tamoxifen
Colchicine
Acetyl esters of carnitine
Pentoxifylline
Phosphodiesterase type 5 inhibitors
Intralesional treatments
Steroids
Verapamil
Clostridium collagenase
Interferon
Topical treatments
Verapamil
Iontophoresis
Extracorporeal shockwave treatment
Traction devices

3.3.2.3.1.1 Oral treatment

Vitamin E

Vitamin E (tocopherol, a fat-soluble compound that acts as a natural antioxidant to reduce the number of oxygen-free radicals produced in energy metabolism) is commonly prescribed by the majority of urologists at once or twice daily doses of 400 IU because of its wide availability, low cost and safety [392]. A double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size [393]. Moreover, there is conflicting evidence as to the long-term cardiovascular effects of vitamin E usage at the large doses, which urologists use for penile deformity treatment [394].

Potassium para-aminobenzoate (Potaba™)

Potassium para-aminobenzoate is thought to exert an antifibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and an enhancement of the activity of monoamine oxidases [395]. Preliminary studies reported an improvement in penile curvature, penile plaque size, and penile pain during erection [396]. In a prospective double-blinded controlled study in 41 patients with PD, Potaba (12 g/day for twelve months) improved penile pain significantly, but not penile curvature or penile plaque size [397]. In another similar study in 103 patients with PD, Potaba decreased penile plaque size significantly, but had no effect on penile curvature or penile pain [398]. However, the pre-existing curvature under Potaba remained stable, suggesting a protective effect on the deterioration of penile curvature. Treatment-related adverse events are nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion and difficulty concentrating, but no serious adverse events were reported [399].

Tamoxifen

Tamoxifen is a non-steroidal oestrogen receptor antagonist modulating transforming growth factor β 1 (TGF β 1) secretion by fibroblasts. Preliminary studies reported that tamoxifen (20 mg twice daily for three months) improved penile pain, penile curvature, and reduced the size of penile plaque [400]. However, a placebo-controlled, randomised study (in only 25 patients, at a late stage of the disease with a mean duration of twenty months) using the same treatment protocol, failed to show any significant improvement in pain, curvature, or plaque size in patients with PD [401].

Colchicine

Colchicine has been introduced into the treatment of PD on the basis of its anti-inflammatory effect [402]. Clinical data should be interpreted with caution since they come from only uncontrolled studies. Preliminary results showed that half of the men given colchicine (0.6-1.2 mg daily for three to five months) found that painful erections and penile curvature improved, while penile plaque decreased or disappeared in 50% of 24 men [403]. In another study in 60 men (colchicine 0.5-1 mg daily for three to five months with escalation to 2 mg twice daily), penile pain resolved in 95% and penile curvature improved in 30% [402]. Similar results have been reported in another uncontrolled retrospective study in 118 patients [404]. Reported treatment-related adverse events with colchicine are gastrointestinal effects (nausea, vomiting, diarrhoea) that can be improved with dose escalation [402].

The combination of vitamin E and colchicine (600 mg/day and 1 mg every twelve hours, respectively for six months) in patients with early-stage PD resulted in significant improvement in plaque size and curvature, but not in pain compared to ibuprofen 400 mg/day for six months [405].

Acetyl esters of carnitine

Acetyl-L-carnitine and propionyl-L-carnitine are proposed to inhibit acetyl coenzyme-A and produce an anti-proliferative effect on human endothelial cells. This may eventually suppress fibroblast proliferation and collagen production, thus reducing penile fibrosis. In a randomised, double-blind study in 48 patients with early-stage PD, patients were randomised to acetyl-L-carnitine (1 g twice daily) compared to tamoxifen (20 mg twice daily). After three months, acetyl-L-carnitine was significantly more effective than tamoxifen in pain and curvature reduction and inhibition of disease progression, but not in penile plaque size reduction (both drugs significantly reduced plaque size) [406]. Tamoxifen induced significantly more side-effects.

Finally, the combination of intralesional verapamil (10 mg weekly for ten weeks) with propionyl-L-carnitine (2 g/day for three months) significantly reduced penile curvature, plaque size, and disease progression compared to intralesional verapamil combined with tamoxifen (40 mg/day) for three months [407].

Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase inhibitor which down-regulates TGF β 1 and increases fibrinolytic activity [408]. Moreover, an increase of NO levels may be effective in preventing progression of PD

or reversing fibrosis [409]. Preliminary data from a case report showed that pentoxifylline (400 mg three times daily for six months) improved penile curvature and the findings on US of the plaque [409]. In another study in 62 patients with PD, pentoxifylline treatment for six months appeared to stabilise or reduce calcium content in penile plaques [410].

Phosphodiesterase type 5 inhibitors

The rationale for the use of PDE5Is in PD comes from animal studies showing that they can reduce the collagen/smooth muscle and collagen III/I ratios and increase the apoptotic index in the PD-like plaque [411]. In a retrospective controlled study, daily tadalafil (2.5 mg for six months) resulted in statistically significant ($p < 0.05$) resolution of septal scar in 69% of patients compared to 10% in the control group (no treatment). However, this study included patients with isolated septal scars without evidence of penile deformity [412]. Therefore, no recommendation can be given for PDE5Is in patients with PD.

3.3.2.3.1.2 Intralesional treatment

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure particularly when a dense or calcified plaque is present.

Steroids

Intralesional steroids are thought to act by opposing the inflammatory milieu responsible for Peyronie's plaque progression via inhibition of phospholipase A2, suppression of the immune response and by decreasing collagen synthesis [413]. In small, non-randomised studies, a decrease in penile plaque size and pain resolution was reported [414, 415]. In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistically significant changes in penile deformity, penile plaque size, and penile pain during erection were reported [416]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [414].

Verapamil

The rationale for intralesional use of verapamil (a calcium channel antagonist) in patients with Peyronie's disease is based on in-vitro research [417, 418]. A number of studies have reported that intralesional verapamil injection may induce a significant reduction in penile curvature and plaque volume [419-423]. These findings suggested that intralesional verapamil injections could be advocated for the treatment of non-calcified acute phase or chronic plaques to stabilise disease progression or possibly reduce penile deformity, although large scale, placebo-controlled trials have not yet been conducted [422]. Side-effects are uncommon (4%). Minor side-effects include nausea, light-headedness, penile pain, and ecchymosis [422]. However, in the only randomised, placebo-controlled study, no statistically significant differences on plaque size, penile curvature, penile pain during erection or plaque 'softening' were reported [424]. Younger age and larger baseline penile curvature were found to be predictive of favourable curvature outcomes in a case-series study [425].

Clostridium collagenase

Clostridium collagenase (CCH) is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the PD plaque [426-428]. Clostridium collagenase is now approved by the FDA for PD in adult men with a palpable plaque and a curvature deformity of at least 30° at the start of therapy. Findings from two independent, double-blind, placebo controlled studies, reveal the efficacy and tolerability of CCH for improving the co-primary outcomes of physical penile curvature and the psychological subject reported PD symptom bother domain of the PDQ in adults with PD. Participants were given up to four treatment cycles of CCH or placebo and were then followed for 52 weeks. Overall, of the 551 treated men with CCH 60.8% were global responders compared with 29.5% of the 281 patients who received the placebo. The most commonly reported side-effects were penile pain, penile swelling, and ecchymosis at the site of injection [427]. The data from these two large RCTs were analysed by subgroups including: baseline penile curvature deformity, PD duration, degree of penile calcification, and baseline erectile function severity with better results in patients with less than 60° of curvature, more than two years of evolution, no calcification in the plaque and good erectile function [429].

Clostridium collagenase was approved by the EMA in 2014 specifying that CCH should be administered by a healthcare professional who is experienced in the treatment of male urological diseases. The Risk Management Plan (RMP) requires participating healthcare professionals to be certified within the programme by enrolling and completing training in the administration of CCH treatment for PD [430].

A recent paper which studied a pooled safety analysis of 1,044 CCH-treated patients from six clinical studies showed that the majority of Peyronie's patients experienced at least one adverse reaction (Global Safety database, 92.5%). Most adverse reactions were localised to the penis or groin and the majority of these events were of a mild or moderate severity. Most of these resolved within fourteen days of the injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered. The most frequently reported treatment-related adverse events in the clinical trials in subjects with PD (Global Safety database) were penile hematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%) [431].

Interferon

Interferon α -2b has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improve the wound healing process from PD plaques in-vitro [432]. Intralesional injections (5 x 10⁶ units of interferon α -2b in 10 mL saline, two times per week for twelve weeks) significantly improved penile curvature, plaque size and density, and pain compared to placebo [433, 434]. Side-effects include myalgias, arthralgia, sinusitis, fever and flu-like symptoms. They can be effectively treated with non-steroidal anti-inflammatory drugs before interferon injection.

Hyaluronic Acid

In a prospective, single-arm, multicentre pilot study, 65 patients underwent a ten week cycle of weekly intraplaque injections with hyaluronic acid. Plaque size significantly decreased, penile curvature decreased in 37%, as well as overall sexual satisfaction and seems preferably indicated in the early (active) phase of the disease [435].

3.3.2.3.1.3 Topical treatments

Topical verapamil

There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea. Verapamil gel has been used in this context [436]. Iontophoresis - now known as transdermal electromotive drug administration (EMDA) - has been introduced to try and overcome limitations on the local uptake of the drugs themselves. Small studies using Iontophoresis with verapamil 5 mg and dexamethasone 8 mg resulted in inconsistent results [437, 438].

H-100 Gel

H-100 Gel is composed of nifedipine, superoxide dismutase and emu oil. Twenty-two patients (PD twelve months duration) were studied in a prospective randomised, double-blind, placebo-controlled study. H-100 showed significant improvement in all PD parameters at six months: mean stretched penile length increase (22.6%, $P = 0.0002$), mean curvature reduction (40.8%, $P = 0.0014$), and mean pain level reduction (85.7%, $P = 0.004$). Placebo group showed no significant improvement except for mean stretched penile length increase (6.8%, $P = 0.009$). Crossover patients from placebo to H-100 showed significant improvement in all parameters: mean stretched penile length increase (17.5%, $P = 0.000007$), mean curvature reduction (37.1%, $P = 0.006$), and mean pain level reduction (40%, $P = 0.17$). Treatment was well tolerated. A self-limited rash was the only side-effect in three patients. Statistically significant improvements in flaccid-stretched penile length, curvature and pain suggest that H-100 is a safe and possibly effective non-invasive, topically applied treatment for acute phase PD [439].

Extracorporeal shockwave treatment

The mechanism of action involved in shockwave treatment (ESWT) for PD is still unclear, but there are two hypotheses. In the first hypothesis, shockwave therapy works by directly damaging and remodelling the penile plaque. In the second hypothesis, shockwave lithotripsy increases the vascularity of the area by generating heat resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption [440]. Most uncontrolled studies failed to show significant improvements in patients with PD [441-443]. In a prospective, randomised, double-blind, placebo-controlled study, four weekly treatment sessions of ESWT, with each session consisting of 2,000 focused shockwaves, resulted in significant improvement only for penile pain [444].

Traction devices

The application of continuous traction in Dupuytren's contracture increases the activity of degradative enzymes [445]. This initially leads to a loss of tensile strength and ultimately to solubilisation. It is followed by an increase in newly synthesised collagen [445]. This concept has been applied in an uncontrolled study, including ten patients with Peyronie's disease. The FastSize Penile Extender was applied as the only treatment for two to eight hours per day for six months [111]. Reduced penile curvature of 10-40° was found in all men with an

average reduction of 33% (range: 51-34°). The stretched penile length increased 0.5-2.0 cm and the erect girth increased 0.5-1.0 cm, with a correction of hinge effect in four out of four men. Treatment can be uncomfortable and inconvenient due to use of the device for two to eight hours daily for an extended period, but has been shown to be tolerated by highly motivated patients [376]. There were no serious adverse events, including skin changes, ulcerations, hypoesthesia or diminished rigidity.

In another prospective study, there was a significant reduction in penile curvature (mean 20° reduction). Erectile function and erection hardness also improved significantly. The percentage of patients who were not able to achieve penetration decreased from 62% to 20% ($p < 0.03$). Importantly, the need for surgery was reduced in 40% of patients who would otherwise have been candidates for surgery and simplified the complexity of the surgical procedure (from grafting to plication) in one in three patients [446].

3.3.2.3.1.4 Summary of evidence and recommendations for non-operative treatment of Peyronie's disease

Summary of evidence	LE
Conservative treatment for PD is primarily aimed at treating patients in the early stage of the disease.	3
Oral treatment with potassium para-aminobenzoate may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation.	1b
Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.	1b
Intralesional treatment with CCH showed significant decreases in the deviation angle, plaque width and plaque length.	1b
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	1b
Topical verapamil gel 15% may improve penile curvature and plaque size.	1b
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.	1b
Extracorporeal shockwave treatment does not improve penile curvature and plaque size, but it may be offered for penile pain.	1b
Intralesional treatment with steroids is not associated with significant reduction in penile curvature, plaque size or penile pain.	2b

Recommendations	LE	GR
Use conservative treatment in patients not fit for surgery or when surgery is not acceptable to the patient.	3	C
Do not use extracorporeal shockwave treatment to improve penile curvature and reduce plaque size.	1b	C
Use penile traction devices and vacuum devices to reduce penile deformity and increase penile length.	2b	C
Do not use intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	1b	B
Do not use oral treatment with vitamin E and tamoxifen for significant reduction in penile curvature or plaque size.	2b	B
Do not offer other oral treatments (acetyl esters of carnitine, pentoxifylline, colchicine).	3	C

3.3.2.3.2 Surgical treatment

Although conservative treatment for PD should resolve painful erections in most men, only a small percentage will experience any significant straightening of the penis. The aim of surgery is to correct curvature and allow satisfactory intercourse. Surgery is indicated in patients with penile curvature that does not allow satisfactory intercourse and which is associated with sexual bother [90]. Patients must have a stable disease for at least three months, although a six to twelve month period has also been suggested [447].

The potential aims and risks of surgery should be discussed with the patient so that he can make an informed decision. Specific issues that should be mentioned during this discussion are the risks of penile shortening, ED, penile numbness, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, and the potential need for circumcision at the time of surgery [378]. Two major types of repair may be considered for both congenital penile curvature and PD: penile shortening and penile lengthening procedures [448].

Penile shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis. Penile lengthening procedures are performed on the concave side of the penis and require the use of a graft. They aim to minimise penile shortening caused by Nesbit or plication of the tunica albuginea or correct complex deformities. Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) is considered the standard approach for all types of procedures [448]. However, recent data suggest that circumcision is not always necessary e.g. in cases where the foreskin is normal pre-operatively [449]. Finally, in patients with PD and ED not responding to medical treatments, surgical correction of the curvature with concomitant penile prosthesis implantation should be considered [450].

Selection of the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of ED [378]. Patient expectations from surgery must also be included in the pre-operative assessment. There are no standardised questionnaires for the evaluation of surgical outcomes [90]. Data from well-designed prospective studies are scarce, with a low level of evidence. Most data are mainly based on retrospective studies, typically non-comparative and non-randomised, or on expert opinion [378, 451].

3.3.2.3.2.1 Penile shortening procedures

In 1965, Nesbit was the first to describe the removal of the tunical ellipses opposite a non-elastic corporal segment to treat congenital penile curvature [452]. Fourteen years later, this technique became a successful treatment option, also for PD [453]. This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or approximately 1 mm for each 10° of curvature [448]. The overall short- and long-term results of the Nesbit operation are excellent. Complete penile straightening is achieved in more than 80% of patients [454]. Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of post-operative ED is minimal [448, 455]. Penile shortening is the most commonly reported outcome of the Nesbit procedure [455]. However, shortening of only 1-1.5 cm has been reported for about 85% of patients, which is rarely the cause of post-operative sexual dysfunction [453, 456]. Patients often perceive the loss of length as greater than it actually is [454, 455]. It is therefore advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used. Only one modification of the Nesbit procedure has been described (partial thickness shaving instead of conventional excision of a wedge of tunica albuginea) [457].

Plication procedures are based on the same principle as the Nesbit operation but are simpler to perform. Many of them have been described as Nesbit modifications in the older literature. They are based on single or multiple longitudinal incisions on the convex side of the penis closed in a horizontal way, applying the Heineke-Miculicz principle, or plication is performed without making an incision [458-463]. Another modification has been described as the '16 dot' technique with minimal tension under local anaesthesia [464]. The use of non-absorbable sutures reduced recurrence of the curvature. Results and satisfaction rates are similar to the Nesbit procedure [448]. However, numerous different modifications have been described and the level of evidence is not sufficient to recommend one method over the other.

3.3.2.3.2.2 Penile lengthening procedures

Tunical lengthening procedures entail an incision in the short (concave) side of the tunica to increase the length of this side, creating a tunical defect, which is covered by a graft. However, plaque removal may be associated with high rates of post-operative ED due to venous leak [465].

Devine and Horton introduced dermal grafting in 1974 [466]. Since then, a variety of grafting materials and techniques have been reported (Table 10) [467-481]. Unfortunately, the ideal material for grafting has yet to be identified. In addition, grafting procedures are associated with ED rates as high as 25%. Despite excellent initial surgical results, graft contracture and long-term failures resulted in a 17% re-operation rate [482].

Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. The Saphenous vein is the most common vein graft used, followed by dorsal penile vein [448]. In the first case, a secondary incision for graft harvesting is avoided. Post-operative curvature (20%), penile shortening (17%) and graft herniation (5%) have been reported after vein graft surgery [472, 477, 480]. Tunica vaginalis is relatively avascular, easy to harvest and has little tendency to contract due to its low metabolic requirements [470].

Dermal grafts are commonly associated with contracture resulting in recurrent penile curvature (35%), progressive shortening (40%), and a 17% re-operation rate at ten years [483]. Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multi-directional elasticity/expansion

by 30% [481]. In a retrospective telephone interview, 44% of patients with pericardium grafting reported recurrent curvature, although most of them continued to have successful intercourse and were pleased with their outcomes [481, 483].

Small intestinal submucosa (SIS, a collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine) has been shown to promote tissue-specific regeneration, and supports the growth of endothelial cells. Small intestinal submucosa acts as a scaffold to promote angiogenesis, host cell migration and differentiation, resulting in tissue structurally and functionally similar to the original. It has been used successfully to repair severe chordee and Peyronie's disease, without significant contraction or histological alterations, but data are limited [478].

More recently the use of buccal mucosa grafts (BMG) has been advocated. Buccal mucosa grafts provided excellent short-term results, suggested by the fast return of spontaneous erections and prevented shrinkage, which is the main cause of graft failure. It also proved to be safe and reproducible, thus representing a valuable treatment option for PD [469].

Grafting by collagen fleece (TachoSil®) in PD is feasible and promising. Major advantages are decreased operative times and easy application. Moreover, an additional haemostatic effect is provided [484].

Tunical incision, preferably with grafting, offers an excellent surgical option for men with curvatures over 60° as well as patients with an hour-glass deformity and good erectile function that are willing to risk a higher rate of post-operative ED [485]. The presence of pre-operative ED, the use of larger grafts, age more than 60 years, and ventral curvature are considered poor prognostic factors for functional outcome after grafting surgery [450]. Although the risk for penile shortening is significantly less compared to the Nesbit or plication procedures, it is still an issue and patients must be informed accordingly [448]. The use of geometric principles introduced by Egydio helps to determine the exact site of the incision, and the shape and size of the defect to be grafted [471].

The use of a penile extender device on an eight to twelve hour daily regimen has been advocated as an effective and safe treatment for loss of penile length in patients operated on for PD [486].

Table 9: Types of grafts used in Peyronie's disease surgery

Autologous grafts
Dermis
Vein grafts
Tunica albuginea
Tunica vaginalis
Temporalis fascia
Buccal mucosa
Allografts
Cadaveric pericardium
Cadaveric fascia lata
Cadaveric dura matter
Cadaveric dermis
Xenografts
Porcine small intestinal submucosa
Bovine pericardium
Porcine dermis
Synthetic grafts
Gore-Tex®
Dacron®
Collagen fleece (TachoSil®)

3.3.2.3.2.3 Penile prosthesis

Penile prosthesis (PP) implantation is typically reserved for the treatment of PD in patients with ED, especially when they are non-responders to PED5Is [376]. Although all types of penile prosthesis can be used, the implantation of inflatable penile prosthesis seems to be most effective in these patients [480].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion. In cases of severe deformity, intra-operative ‘modelling’ of the penis over the inflated cylinders (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) has been introduced as an effective treatment [487, 488]. If there is a residual curvature of less than 30°, no further treatment is recommended, as the prosthesis will act as a tissue expander and will result in complete correction of curvature after a few months of cycling the prosthesis [487]. While this technique is effective in most patients, a Nesbit/plication procedure or plaque excision/incision and grafting may be required in order to achieve adequate straightening [489-491].

The risk of complications (infection, malformation, etc.) is not increased compared to the general population. However, a small risk of urethral perforation (3%) has been reported in patients with ‘modelling’ over the inflated prosthesis [488].

In selected cases of end-stage PD with ED and significant penile shortening, a lengthening procedure, which involves simultaneous PP implantation and penile length restoration, such as the ‘sliding’ technique, can be considered but only in the hands of experienced high-volume surgeons [492].

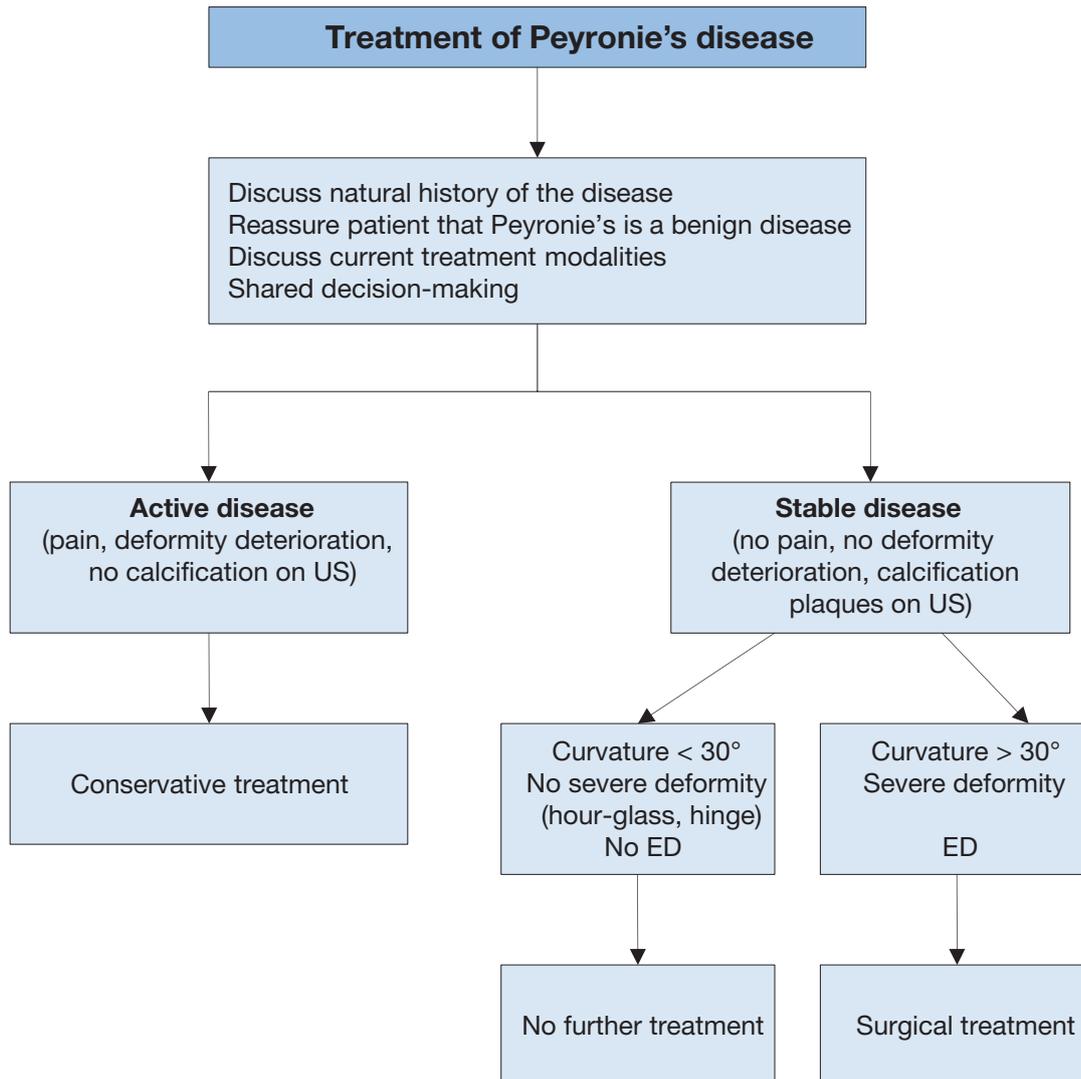
Table 10: Results of surgical treatments for Peyronie’s disease (data from different, non-comparable studies) [453, 455-481, 483, 485]

	Tunical shortening procedures		Tunical lengthening procedures
	Nesbit	Plication	Grafts
Penile shortening	4.7-30.8%	41-90%	0-40%
Penile straightening	79-100%	58-100%	74-100%
Persistent or recurrent curvature	4-26.9%	7.7-10.6%	0-16.7%
Post-operative erectile dysfunction	0-13%	0-22.9%	0-15%
Penile hypoesthesia	2-21%	0-21.4%	0-16.7%
Technical modifications	1	At least 3	Many types of grafts and techniques used

Treatment algorithm

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of the curvature and erectile function status. If the degree of curvature is less than 60°, penile shortening is acceptable and the Nesbit or plication procedures are usually the method of choice. This is typically the case for congenital penile curvature. If the degree of curvature is over 60° or is a complex curvature, or if the penis is significantly shortened in patients with a good erectile function (with or without pharmacological treatment), then a grafting procedure is feasible. If there is ED, which is not responding to pharmacological treatment, the best option is the implantation of an inflatable PP, with or without an associated procedure over the penis (modelling, plication or even grafting plus the prosthesis). The treatment algorithm is presented in Figure 5.

Figure 5: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; US = ultrasound.

The results of the different surgical approaches are presented in Table 10. It must be emphasised that there are no RCTs available addressing surgery in PD. The risk of ED seems to be greater for penile lengthening procedures [378, 448]. Recurrent curvature implies either failure to wait until the disease has stabilised, a re-activation of the condition following the development of stable disease, or the use of re-absorbable sutures that lose their strength before fibrosis has resulted in acceptable strength of the repair [120]. Accordingly, it is recommended that only non-absorbable sutures or slowly re-absorbed absorbable sutures be used. Although with non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin but this issue may be alleviated by the use of slowly re-absorbed absorbable sutures [455]. Penile numbness is a potential risk of any surgical procedure involving mobilisation of the dorsal neurovascular bundle. This will usually be a neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure [448].

3.3.2.3.2.4 Recommendations for the surgical treatment of penile curvature

Recommendations	LE	GR
Perform surgery only when Peyronie's disease has been stable for at least three months (without pain or deformity deterioration), which is usually the case after twelve months from the onset of symptoms, and intercourse is compromised due to deformity.	3	C
Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction) and patient expectations.	3	C
Use tunical shortening procedures, especially plication techniques as the first treatment option for congenital penile curvature and for Peyronie's disease with adequate penile length, curvature < 60° and absence of special deformities (hour-glass, hinge).	2b	B
Use grafting techniques for patients with Peyronie's disease and normal erectile function, with no adequate penile length, curvature > 60° and presence of special deformities (hour-glass, hinge).	2b	B
Use penile prosthesis implantation, with or without any additional procedure (modelling, plication or grafting), in Peyronie's disease patients with erectile dysfunction not responding to pharmacotherapy.	2b	B

3.4 Priapism

3.4.1 *Ischaemic (Low-Flow or Veno-Occlusive) Priapism*

3.4.1.1 *Epidemiology/aetiology/pathophysiology*

Ischaemic priapism is the most common form of priapism, accounting for more than 95% of all priapism episodes [493, 494]. It is usually painful, with a rigid erection characterised clinically by absent or reduced intracavernous arterial inflow (often proximally there is a compensated high velocity picture with little flow distally). In ischaemic priapism, there are time-dependent alterations in the corporal metabolic environment, progressively leading to hypoxia, hypercapnia, glucopenia and acidosis [495].

Ischaemic priapism beyond four hours is considered the same as a compartment syndrome, characterised by supraphysiological pressure within the closed space of the corpora cavernosa, which severely compromises cavernous circulation. Emergency medical intervention is required to minimise potential irreversible consequences, such as smooth muscle necrosis, corporal fibrosis and permanent ED [496, 497]. The duration of priapism represents the most significant predictor for the development of ED. In this context, interventions beyond 48-72 hours of onset may help to relieve the erection and pain, but have little benefit in preventing long-term ED.

Histologically, by twelve hours, corporal smooth muscle biopsies show interstitial oedema, progressing to destruction of the sinusoidal endothelium, exposure of the basement membrane and thrombocyte adherence at 24 hours. At 48 hours, thrombi can be found in the sinusoidal spaces and smooth muscle necrosis with fibroblast-like cell transformation is evident [422]. In terms of the pathophysiology (Table 11), no specific cause can be identified in the majority of cases [494, 498]. However, ischaemic priapism can be associated with sickle cell disease, haematological dyscrasias, neoplastic syndromes, and with the use of a number of pharmacological agents. Ischaemic priapism may occur (0.4-35%) after intracavernous injections of erectogenic agents [194, 494, 496, 499, 500]. The risk is highest with papaverine-based combinations, while the risk of priapism is < 1% following prostaglandin E1 injection [501].

Since their introduction on the market, a few cases of priapism have been described in men who have taken PDE5Is [494]. Most of these men however, had other risk factors for priapism, and it is unclear whether PDE5Is alone can cause ischaemic priapism [494]. Since most men who experienced priapism following PDE5I use had additional risk factors for ischaemic priapism, PDE5I use is usually not regarded a risk factor in itself. Sickle cell disease is the most common cause in childhood, accounting for 63% of the cases. It is the primary aetiology in 23% of adult cases [501], with a lifetime probability of developing ischaemic priapism of 29-42% in men with sickle cell disease [501-503] (LE: 4). Mechanisms of sickle cell disease associated priapism may involve dysfunctional NO synthase and Rho-associated protein kinase (ROCK) signaling, and increased oxidative stress associated with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase mediated signaling [504].

Priapism resulting from metastatic or regional infiltration is rare and usually reflects an infiltrative process [505]. As such, the recommendations for pharmacological treatment are unlikely to work and certainly all of these men should have a magnetic resonance imaging (MRI) scan of the penis and be offered supportive care and medical intervention for their primary cancer.

Priapism in children is extremely rare and is most commonly related to malignancy, haematological or otherwise. The investigative focus should be on identifying any underlying causes.

Partial priapism, or idiopathic partial segmental thrombosis of the corpus cavernosum, is a very rare condition. It is often classified as subtype of priapism limited to a single crura but ischaemia does not develop, rather it is a thrombus within the corpus. Its aetiology is unknown, but bicycle riding, trauma, drug usage, sexual intercourse, haematological diseases and α -blockers have been associated with partial priapism [506]. There may be a congenital web in the corpora which poses a risk factor [507].

Table 11: Potential causative factors for ischaemic priapism

Idiopathic
Haematological dyscrasias (sickle cell disease, thalassemia, leukaemia; multiple myeloma, Hb Olmsted variant, fat emboli during hyperalimentation, haemodialysis, glucose-6-phosphate dehydrogenase deficiency, Factor V Leiden mutation)
Infections (toxin-mediated) (i.e. scorpion sting, spider bite, rabies, malaria)
Metabolic disorders (i.e. amyloidosis, Fabry's disease, gout)
Neurogenic disorders (i.e. syphilis, spinal cord injury, cauda equina syndrome, autonomic neuropathy, lumbar disc herniation, spinal stenosis, cerebrovascular accident, brain tumour, spinal anaesthesia)
Neoplasms (metastatic or regional infiltration) (i.e. prostate, urethra, testis, bladder, rectal, lung, kidney)
Medications
- Vasoactive erectile agents (i.e. papaverine, phentolamine, prostaglandin E1/alprostadil, combination of intracavernous therapies)
- α -adrenergic receptor antagonists (i.e. prazosin, terazosin, doxazosin, tamsulosin)
- Anti-anxiety agents (hydroxyzine)
- Anticoagulants (heparin, warfarin)
- Antidepressants and antipsychotics (i.e. trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thiorizadine, phenothiazines)
- Antihypertensives (i.e. hydralazine, guanethidine, propranolol)
- Hormones (i.e. gonadotropin-releasing hormone, testosterone)
- Recreational drugs (i.e. alcohol, marijuana, cocaine [intranasal and topical], crack, cocaine)

3.4.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of ischaemic priapism

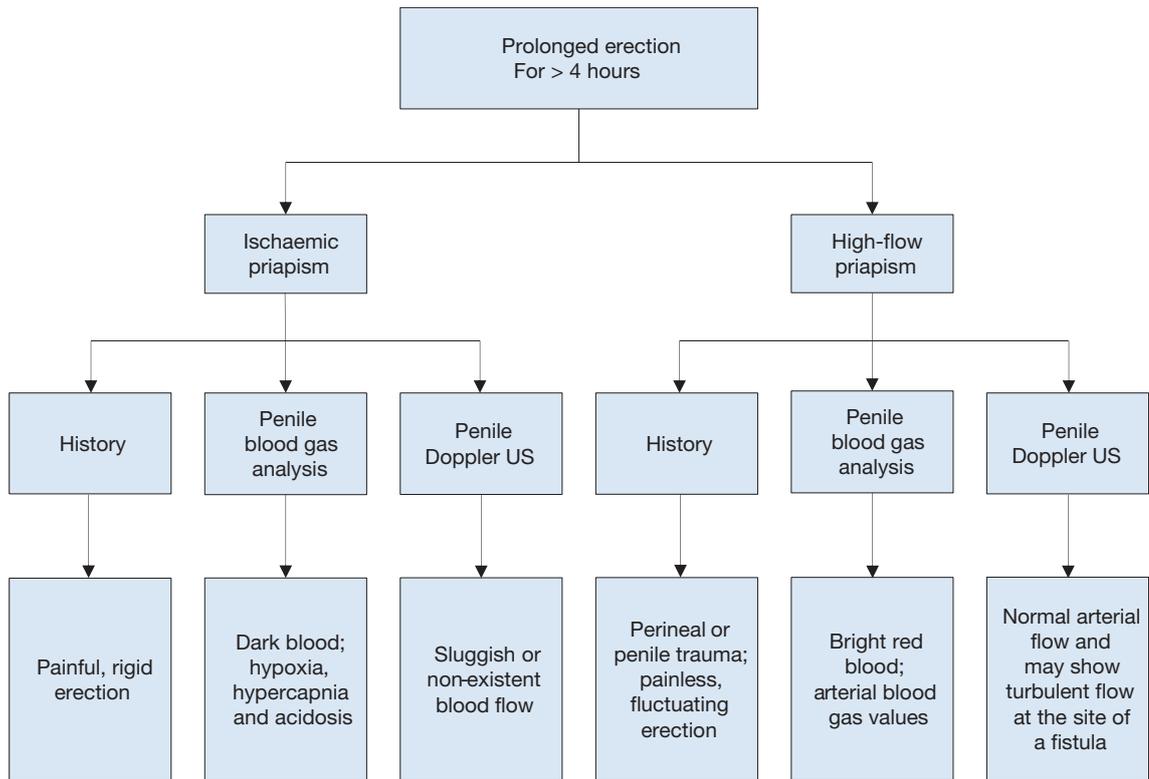
Summary of evidence	LE
Ischaemic priapism is most common, accounting for more than 95% of all cases.	1b
Ischaemic priapism is identified as idiopathic in the vast majority of patients, while sickle cell anaemia is the most common cause in childhood.	1b
Ischaemic priapism occurs relatively often (up to 35%) after intracavernous injections of papaverine based combinations, while it is rare (< 1%) after prostaglandin E1 monotherapy.	2a
Priapism is rare in men who have taken PDE5Is with only sporadic cases reported.	1a

3.4.1.2 Classification

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow [494]. The patient typically complains of penile pain and examination reveals a rigid erection. Resolution of ischaemic priapism is characterised by return to a flaccid non-painful state. However, in many cases, persistent penile oedema, ecchymosis and partial erections can occur and may mimic unresolved priapism. The partial erections may reflect reactive hyperaemia and are sometimes misdiagnosed as persistent priapism. When left untreated, resolution may take days and ED invariably results.

3.4.1.3 Diagnostic evaluation

Figure 6: Differential diagnosis of priapism



3.4.1.3.1 History

Taking a comprehensive history is the mainstay in priapism diagnosis [494, 508]. The medical history must include asking about a history of sickle cell disease or any other haematological abnormality [9, 509] and a history of pelvic, genital or perineal trauma. The sexual history must include complete details of the duration of the erection, the presence and degree of pain, prior medical drug use, any previous history of priapism and erectile function prior to the last priapism episode (Table 12). The history can help to determine the underlying subtype of priapism (Table 13). Ischaemic priapism is classically associated with progressive penile pain and the erection is rigid.

Table 12: Key points in taking the history of priapism (adapted from Broderick et al. [494])

Duration of erection
Presence and degree of pain
Previous episodes of priapism and method of treatment
Current erectile function, especially the use of any erectogenic therapies prescription or nutritional supplements
Medications and recreational drugs
Sickle cell disease, haemoglobinopathies, hypercoagulable states
Trauma to the pelvis, perineum, or penis

3.4.1.3.2 Physical examination

In ischaemic priapism, the corpora are fully rigid and tender, but the glans penis is soft. The patient complains of pain. Pelvic examination may reveal cases of underlying malignancy.

3.4.1.3.3 Laboratory testing

Laboratory testing should include a complete blood count, white blood count with blood cell differential, platelet count and coagulation profile to assess anaemia and detect haematological abnormalities [494, 508].

Blood aspiration from the corpora cavernosa shows dark ischaemic blood (Table 13) (LE: 2b). Blood gas analysis is essential to differentiate between ischaemic and arterial priapism (Table 14). Further laboratory

testing should be directed by history, clinical and laboratory findings. These may include specific tests for the diagnosis of sickle cell anaemia or other haemoglobinopathies (e.g. haemoglobin electrophoresis) or urine and plasma toxicological studies when there is suspected use of recreational psychoactive drugs.

3.4.1.3.4 Penile imaging

Colour Doppler US of the penis and perineum is recommended and can differentiate ischaemic from arterial priapism as an alternative or adjunct to blood gas analysis [510-512] (LE: 2b). Scanning of the penis should be performed before corporal blood aspiration in ischaemic priapism.

Examination of the penile shaft and perineum is recommended. In ischaemic priapism there will be an absence of blood flow in the cavernous arteries. The return of the cavernous artery waveform will result in successful detumescence [494, 512, 513]. After aspiration, a reactive hyperaemia may develop with a high arterial flow proximally that may mislead the diagnosis as arterial priapism.

The role of MRI in the diagnostic evaluation of priapism is controversial. It may be helpful in cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In a prospective study in 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, as confirmed by corporal biopsy [514]. In this study, all patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up (LE: 3).

Table 13: Key findings in priapism (adapted from Broderick *et al.* [494])

	Ischaemic priapism	Arterial priapism
Corpora cavernosa fully rigid	Usually	Seldom
Penile pain	Usually	Seldom
Abnormal penile blood gas	Usually	Seldom
Haematological abnormalities	Usually	Seldom
Recent intracorporeal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Usually

Table 14: Typical blood gas values (adapted from Broderick *et al.* [494])

Source	pO ₂ (mmHg)	pCO ₂ (mmHg)	pH
Normal arterial blood (room air) [similar values are found in arterial priapism]	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

3.4.1.3.5 Recommendations for the diagnosis of ischaemic priapism

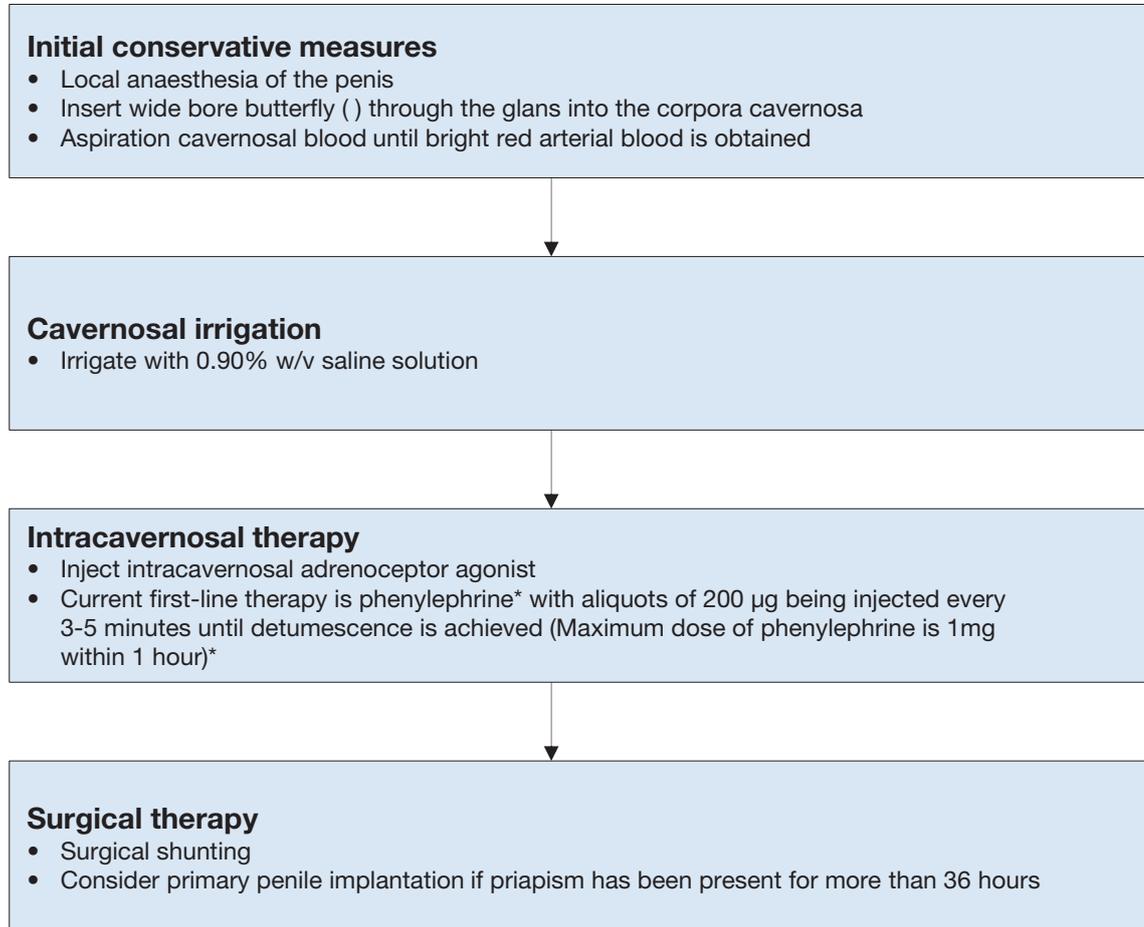
Recommendations	GR
Take a comprehensive history for diagnosis which can help to determine the underlying type of priapism.	B
Include physical examination of the genitalia, the perineum and the abdomen in the diagnostic evaluation.	B
For laboratory testing, include complete blood count, white blood count with blood cell differential, platelet count and coagulation profile. Direct further laboratory testing by history, clinical and laboratory findings. In children with priapism, perform a complete evaluation of all possible causes.	B
Analyse blood gas of blood aspirated from the penis for the differentiation between ischaemic and arterial priapism.	B
Perform colour duplex ultrasound of the penis and perineum for the differentiation between ischaemic and arterial priapism as an alternative or adjunct to blood gas analysis.	B
In cases of prolonged ischaemic priapism, use magnetic resonance imaging of the penis to predict smooth muscle viability and confirm erectile function restoration.	B
Perform selected pudendal arteriogram when embolisation is planned for the management of arterial priapism.	B

3.4.1.4 Disease management

Acute ischaemic priapism is a medical emergency. Urgent intervention is compulsory (LE: 4), and should follow a stepwise approach. The aim of any treatment is to restore penile flaccidity, without pain, in order to prevent damage to the corpora cavernosa.

Figure 7: Treatment of ischaemic priapism

The treatment is sequential and the physician should move on to the next stage if the treatment fails.



(*) The dose of phenylephrine should be reduced in children. It can result in significant hypertension and should be used with caution in men with cardiovascular disease and monitoring of pulse, blood pressure and electrocardiogram (ECG) is advisable in all patients during administration and for 60 minutes afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

3.4.1.4.1 First-line treatments

First-line treatments in ischaemic priapism of more than four hours duration are strongly recommended before any surgical treatment (LE: 4). Conversely, first-line treatments initiated beyond 72 hours while relieving the priapism have little documented benefit in terms of long-term potency preservation (LE: 4).

Historically, several first-line treatments have been described including exercise, ejaculation, ice packs, cold baths, and cold water enemas [494]. However, there is lack of evidence of benefit for such measures.

Partial priapism usually resolves spontaneously with analgesic treatment while surgical intervention is rarely needed [515].

3.4.1.4.1.1 Penile anaesthesia/systemic analgesia

It is possible to perform blood aspiration and intracavernous injection of a sympathomimetic agent without any anaesthesia. However, anaesthesia may be necessary when there is severe penile pain. While it is recognised that the anaesthesia may not alleviate the ischaemic pain, cutaneous anaesthesia will facilitate subsequent therapies. The treatment options for penile anaesthesia/systemic analgesia include:

- dorsal nerve block;
- circumferential penile block;
- subcutaneous local penile shaft block;
- oral conscious sedation (for paediatric patients).

3.4.1.4.1.2 Aspiration ± irrigation with 0.9% w/v saline solution

The first intervention for an episode of priapism lasting more than four hours consists of corporal aspiration (LE: 4) to drain stagnant blood from the corporal bodies, making it possible to relieve the compartment syndrome-like condition of the penis. Blood aspiration may be performed with intracorporeal access either through the glans or via percutaneous needle access on the lateral aspect of the proximal penile shaft, using a 16 G or 18 G angiocatheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain the corpus cavernosum (LE: 4).

Some clinicians use two angiocatheters or butterfly needles at the same time to accelerate drainage, as well as aspirating and irrigating simultaneously with a saline solution [502] (LE: 4). Aspiration should be continued until fresh red, oxygenated, blood is aspirated (LE: 4).

This approach has up to a 30% chance of resolving the priapism. There are insufficient data to determine whether aspiration followed by saline intracorporeal irrigation is more effective than aspiration alone (LE: 4).

3.4.1.4.1.3 Aspiration ± irrigation with 0.90% w/v saline solution in combination with intracavernous injection of pharmacological agents.

This combination is currently considered the standard of care in the treatment of ischaemic priapism [4, 494, 516] (LE: 4). Pharmacological agents include sympathomimetic drugs or α -adrenergic agonists. Options for intracavernous sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80%. [494, 516-524] (LE: 2b). The use of intracavernous adrenaline injection alone has also been sporadically reported [525].

Phenylephrine

Phenylephrine is currently the drug of choice due to its high selectivity for the α -1-adrenergic receptor, without concomitant β -mediated inotropic and chronotropic cardiac effects [517, 521, 522] (LE: 4).

Phenylephrine is diluted in normal saline to a concentration of 100-500 μ g/mL. Usually 200 μ g are given every three to five minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within one hour (LE: 4). A lower concentration or volume is applicable for children and patients with severe cardiovascular disease (LE: 4).

Phenylephrine use has potential cardiovascular side-effects [494, 516-518, 521, 522] and it is recommended that blood pressure and pulse are monitored every fifteen minutes for an hour after the injection. This is particularly important in older men with existing cardiovascular diseases. After injection, the puncture site should be compressed and the corpora cavernosa massaged to facilitate drug distribution.

The potential treatment-related side-effects of intracavernous phenylephrine (and other sympathomimetic agents) include headache, dizziness, hypertension, reflex bradycardia, tachycardia and palpitations, irregular cardiac rhythms and sporadic subarachnoid haemorrhage [39]. Monitoring of blood pressure and pulse with ECG should be performed during intracavernous administration of sympathomimetic agents.

Overall, the administration of intracavernous sympathomimetic agents is contraindicated in patients suffering from malignant or poorly controlled hypertension and in those who are concurrently taking monoamine oxidase inhibitors (LE: 4).

Etilephrine

Etilephrine is the second most widely used sympathomimetic agent, administered by intracavernous injection at a concentration of 2.5 mg in 1-2 mL normal saline [518] (LE: 3).

Methylene blue

Methylene blue is a guanylate cyclase inhibitor, which may be a potential inhibitor of endothelial-mediated cavernous relaxation. It has therefore been suggested for treating short-term pharmacologically induced priapism [526, 527] (LE: 3). Methylene blue, 50-100 mg [526], should be injected intracavernously and left for five minutes. It is then aspirated and the penis compressed for an additional five minutes [527]. Treatment-related side-effects include a transient burning sensation and blue discolouration of the penis.

Adrenaline

Intracavernosal adrenaline (dosage of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period [525]), has been used in patients with ischaemic priapism due to an intracavernous injection of vasoactive agents. A success rate of over 50% after a single injection, with an overall success rate of 95% with repeated injections is achieved (LE: 3).

Oral terbutaline

Oral terbutaline is a β -2-agonist with minor β -1 effects and some α -agonist activity. A dose of 5 mg has been suggested to treat prolonged erections lasting more than 2.5 hours, after intracavernous injection of vasoactive agents, although the mechanism of action is not yet fully understood [528-530] (LE: 1b). Its main use is in the prevention of recurrent episodes of prolonged erection. Terbutaline should be given cautiously in patients with coronary artery disease, increased intravascular fluid volume, oedema and hypokalaemia [530].

Table 15: Medical treatment of ischaemic priapism

Drug	Dosage/Instructions for use
Phenylephrine	<ul style="list-style-type: none"> Intracavernous injection of 200 μg every three to five minutes. Maximum dosage is 1 mg within one hour. The lower doses are recommended in children and patients with severe cardiovascular disease.
Etilephrine	<ul style="list-style-type: none"> Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL normal saline.
Methylene blue	<ul style="list-style-type: none"> Intracavernous injection of 50-100 mg, left for five minutes. It is then aspirated and the penis compressed for an additional five minutes.
Adrenaline	<ul style="list-style-type: none"> Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a twenty-minute period.
Terbutaline	<ul style="list-style-type: none"> Oral administration of 5 mg for prolonged erections lasting more than 2.5 hours, after intracavernous injection of vasoactive agents.

Management of sickle cell disease related priapism

Rapid intervention is essential (LE: 4) and the general approach is similar to that described in other cases of ischaemic priapism and should be co-ordinated with a haematologist [531-533] (LE: 4).

However, as with other haematological disorders, other therapeutic practices may also need to be implemented [531, 533, 534]. Specific measures for sickle cell disease related priapism include intravenous hydration and parental narcotic analgesia while preparing the patient for aspiration and irrigation. In addition, supplemental oxygen administration and alkalinisation with bicarbonate can be helpful [503, 532].

Exchange blood transfusion has also been proposed, with the aim of increasing the tissue delivery of oxygen [535]. The transfused blood should be HbS negative, Rh and Kell antigen matched [536]. However, the evidence is inconclusive as to whether exchange transfusion itself helps to resolve the priapism in these men. It should also be noted that several reports suggest that this treatment may result in serious neurological sequelae [537]. Because of these considerations, the routine use of this therapy is not recommended (LE: 4).

3.4.1.4.2 Second-line treatments

Second-line intervention typically refers to surgical intervention in the form of penile shunt surgery and should only be considered when conservative management options fail (LE: 4). There is no evidence detailing the amount of time allowed for first-line treatment before moving on to surgery. Consensus recommendations suggest a period of at least one hour of first-line therapy prior to moving to surgery (LE: 4). A number of clinical indicators suggest failure of first-line treatment including continuing corporal rigidity, cavernosal acidosis and anoxia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressures by pressure monitoring (LE: 4).

3.4.1.4.3 Penile shunt surgery

Penile shunt surgery aims to produce an exit for ischaemic blood from the corpora cavernosa thereby allowing the restoration of normal circulation within these structures. Accordingly, any shunt creates an opening in the tunica albuginea, which may communicate with either the glans, the corpus spongiosum or a vein for blood drainage [494, 516, 538].

In general, the type of shunt procedure chosen is according to the surgeon's preference and familiarity with the procedure. It is conventional for distal shunt procedures to be tried before proximal shunting is considered (LE: 4). Cavernous biopsy has been used to identify smooth muscle necrosis (which, if present, would suggest that shunting is likely to fail) although this is mainly performed for medico-legal purposes and patient counselling.

It is important to assess the success of surgery by either direct observation or by investigation (e.g. cavernous blood gas testing, penile colour duplex US) (LE: 4) [494, 516].

The recovery rates of erectile function in men undergoing shunt surgery for prolonged erections are low and directly relate to the duration of the priapism [539, 540]. Priapism for more than 36 hours appears to irreversibly impair erectile tissue both structurally and functionally [539]. In general, shunt procedures undertaken after this time period may only serve to limit pain without any benefit for erectile function (LE: 4) [541, 542].

Four categories of shunt procedures have been reported [4, 494, 538, 542]. The limited available data preclude any recommendation for one procedure over another based on outcome (LE: 4).

Percutaneous distal (corpora-glanular) shunts

Winter's procedure: this procedure uses a Trucut biopsy needle to create a fistula between the glans penis and each corpora cavernosa [4, 494, 501, 543, 544] (LE: 3). Post-operative sequelae are uncommon [545]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [540].

Ebbehoj's technique: this technique involves making multiple tunical incision windows between the glans and each tip of the corpus cavernosum by means of a size 11 blade scalpel passed several times percutaneously [4, 494, 543, 546, 547] (LE: 3).

T-Shunt: this technique involves performing a bilateral procedure using a size 10 blade scalpel placed vertically through the glans just lateral to the meatus until fully within the corpus cavernosum. The blade is then rotated 90° away from the urethra and pulled out [4, 494, 543, 548] (LE: 3). This is followed by a tunneling procedure using a size 8 dilator inserted through the glans and into the corpora which can be performed using US for guidance, mainly in order to avoid urethral injury [548].

Open distal (corpora-glanular) shunts

Al-Ghorab's procedure: this procedure consists of an open bilateral excision of circular cone segments of the distal tunica albuginea via the glans penis, along with a subsequent glans closure by means of a running suture with absorbable material [4, 494, 543, 549, 550] (LE: 3).

Burnett's technique (Snake manoeuvre): a modification of the Al-Ghorab corpora-glanular shunt surgery involves the retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glanular excision. After removal of the dilator from the corpus cavernosum, blood evacuation is facilitated by manual compression of the penis sequentially from a proximal to distal direction. After detumescence, the glans penis skin is closed as in the Al-Ghorab procedure [4, 494, 543, 551, 552] (LE: 3). Reported complications include wound infection, penile skin necrosis and a urethrocutaneous fistula [552].

Open proximal (corporospongiosal) shunts

Quackles's technique: through a trans-scrotal or perineal approach, a proximal open shunt technique creates a communication between the corpus cavernosum and the corpus spongiosum. The most frequent complications include an unwanted urethro-cavernous fistula and urethral stricture or the development of cavernositis [4, 494, 538, 553]. The risk of urethral injury is less with a perineal approach to the bulb of the corpus spongiosum (LE: 3).

Vein anastomoses/shunts

Grayhack's procedure: this mobilises the saphenous vein below the junction of the femoral vein and anastomoses the vein end-to-side onto the corpus cavernosum. Venous shunts may be complicated by saphenofemoral thrombus formation and by pulmonary embolism [4, 494, 554-556] (LE: 3).

Immediate surgical prosthesis implantation

Refractory, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48-72 hours usually result in complete ED, possibly along with major penile deformity. In these cases, immediate penile prosthesis surgery has been suggested [557-560] (LE: 3).

The immediate insertion of a malleable penile prosthesis has been recommended to avoid the difficulty and complications of delayed surgery in the presence of corporal fibrosis. Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and cavernositis [557, 559], along with a small rate of revision surgery [557]. Early surgery also offers the opportunity to maintain penile size, and prevent penile curvature due to cavernosal fibrosis. The prosthesis can be exchanged for an inflatable prosthesis at a later date which also allows upsizing of the implant cylinders [561].

Currently, there are no clear indications for immediately implanting a penile prosthesis in a man with acute ischaemic priapism [516]. Relative indications include [494] (LE: 4):

- ischaemia that has been presented for more than 36 hours [560];
- failure of aspiration and sympathomimetic intracavernous injections;
- failure of distal and proximal shunting (although in delayed cases, implantation might be considered ahead of shunt surgery);
- Magnetic resonance imaging or corporal biopsy evidence of corporal smooth muscle necrosis [494, 557] (LE: 4).

Surgery for non-acute sequelae after ischaemic priapism

Structural changes may occur after ischaemic priapism including cavernosal tissue necrosis and fibrosis with consequent penile scarring, megalophallic deformities, penile shortening, and occasional penile loss, [538, 557, 562, 563]. Erectile dysfunction is also often observed [494, 564]. Unfortunately, these outcomes can still occur despite apparently successful first-line or second-line treatment.

Prosthesis implantation is occasionally indicated in sickle cell patients with severe ED since other therapeutic options such as PDE5Is and intracavernous injections are avoided as they may provoke a further priapism event [494, 516]. In severe corporal fibrosis, semi-rigid prosthetic devices are preferable to inflatable implants [557, 565] (LE: 3). Following severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, penile reconstruction and concomitant prosthesis implant may be considered [566] (LE: 3).

3.4.1.5 Summary of evidence and recommendations for the treatment of ischaemic priapism

Summary of evidence	LE
Intervene rapidly for ischaemic priapism, which is an emergency condition.	2b
Treatment aims to restore painless penile flaccidity, in order to prevent chronic damage to the corpora cavernosa.	3
Erectile function preservation is directly related to the duration of ischaemic priapism.	2b
Phenylephrine is the recommended drug due to its favourable safety profile on the cardiovascular system compared to other drugs. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 µg/mL and given in 200 µg doses every three to five minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within one hour. Patients at high cardiovascular risk should be given lower doses. Patient monitoring is highly recommended.	2b
The efficacy of shunt procedures for ischaemic priapism is questionable. Diagnose smooth muscle necrosis when needed with cavernous biopsy. No clear recommendation on one type of shunt over another can be given.	3
Erectile dysfunction is inevitable in prolonged cases or priapism. Implantation of penile prosthesis at a later stage can be difficult due to severe corporal fibrosis.	2b

Recommendations	GR
Start management of ischaemic priapism as early as possible (within four to six hours) and follow a stepwise approach.	B
First, decompress the corpora cavernosa by penile aspiration until fresh red blood is obtained.	C
In priapism secondary to intracavernous injections of vasoactive agents, replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step.	C
In priapism that persists despite aspiration, proceed to the next step, which is intracavernous injection of a sympathomimetic drug.	B
In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, repeat these steps several times before considering surgical intervention.	C
Treat ischaemic priapism due to sickle cell anaemia in the same fashion as idiopathic ischaemic priapism. Provide other supportive measures (intravenous hydration, oxygen administration with alkalinisation with bicarbonates, blood exchange transfusions), but do not delay initial treatment to the penis.	B
Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed or for priapism events lasting < 72 hours.	C
Perform distal shunt surgical procedures first followed by proximal procedures in case of failure.	C
Discuss the immediate implantation of a penile prosthesis with the patient in cases of priapism presenting > 36 hours after onset, or in cases for which all other interventions have failed.	B

3.4.1.6 Follow-up

Follow-up of ischaemic priapism after successful treatment should include modification of risk factors (if any) in order to avoid a new event and assessment of erectile function since it may be severely compromised especially after surgical treatment with a shunt. Penile fibrosis is usually easily identified with clinical examination of the penis.

3.4.2 Arterial (high-flow or non-ischaemic) priapism

3.4.2.1 Epidemiology/aetiology/pathophysiology

Epidemiological data on arterial priapism are almost exclusively derived from small case series [494, 512, 513, 567, 568]. The most frequent cause of high-flow priapism is blunt perineal or penile trauma [569]. The injury results in a laceration in the cavernosal artery leading to a high-flow fistula between the artery and the lacunar spaces of the sinusoidal tissue [568]. This unregulated flow results in a persistent erection, and has been proposed to occur via a mechanism that involves stimulation of endothelial NO synthase by the turbulent blood flow [570]. Partial erections are enhanced after sexual stimulation, as the trabecular smooth muscle fully relaxes, activating the corporal veno-occlusive mechanism [568, 571].

There is often a delay between the injury and the development of the priapism that may be up to two to three weeks [571]. This has been suggested to reflect either spasm or ischaemic necrosis of the injured artery, with the fistula only developing as the spasm resolves or when the ischaemic segment blows out.

Occasional cases are associated with metastatic malignancy to the penis [572, 573], with acute spinal cord injury [574] and occasionally following intracavernous injections or aspiration due to a lacerated cavernous artery or branch [575, 576]. Under these circumstances, it may complicate low-flow priapism. It has also been reported to occur following internal urethrotomy [577] and a Nesbit procedure [578]. Although sickle cell disease is usually associated with low-flow priapism, occasional cases of high-flow priapism have been reported [579].

3.4.2.1.1 Summary of Evidence on the epidemiology, aetiology and pathophysiology of arterial priapism

Summary of evidence	LE
Arterial priapism usually occurs after blunt perineal or penile trauma.	2

3.4.2.2 Classification

Arterial priapism is a persistent erection caused by unregulated cavernous arterial inflow [494]. The patient typically reports an erection that is not fully rigid and is not associated with pain although fully rigid erections may occur with sexual stimulation.

3.4.2.3 *Diagnostic evaluation*

3.4.2.3.1 History

A comprehensive history is also mandatory in arterial priapism diagnosis and follows the same principles as described in Table 12. Arterial priapism is suspected when there is no pain and erections are not fully rigid (Table 13). It can be associated with full erections under sexual stimulation and when there is a history of coital trauma or blunt trauma to the penis. The onset of post-traumatic high-flow priapism in adults and children may be delayed by hours to days following the initial injury. Sexual intercourse is usually not compromised.

3.4.2.3.2 Physical examination

In arterial priapism, the corpora are tumescent but not fully rigid (Table 13). Abdominal, penile and perineal examination may reveal evidence of trauma.

3.4.2.3.3 Laboratory testing

Blood aspiration from the corpora cavernosa shows bright red arterial blood in arterial priapism, while blood is dark in ischaemic priapism (Table 13) (LE: 2b). Blood gas analysis is essential to differentiate between arterial and ischaemic priapism (Table 14).

3.4.2.3.4 Penile imaging

Colour duplex US of the penis and perineum is recommended and can differentiate arterial from ischaemic priapism as an alternative or adjunct to blood gas analysis [510-512] (LE: 2b). Examination of the penile shaft and perineum is recommended. In arterial priapism US will show turbulent flow at the fistula, which helps to localise the site of trauma since patients with arterial priapism have normal to high blood velocities in the cavernous arteries.

A selective pudendal arteriogram can reveal a characteristic blush at the site of the injury to the cavernosal artery in arterial priapism [580, 581]. However, due to its invasiveness it should be reserved for the management of arterial priapism, when embolisation is being considered [494, 508] (LE: 3).

The role of MRI in the diagnostic evaluation of priapism is controversial. In arterial priapism, its role is limited since the small penile vessels and arteriovenous fistulae cannot be easily demonstrated [582].

3.4.2.3.5 Recommendations for the diagnosis of arterial priapism

The same recommendations as in section 3.4.1.3.5 apply.

3.4.2.4 *Disease management*

The management of high-flow priapism is not an emergency because the penis is not ischaemic. Definitive management can therefore be considered and should be discussed with the patient so that they understand the risks and complications of treatment [494, 508] (LE: 3).

3.4.2.4.1 Conservative management

This may include applying ice to the perineum or site-specific perineal compression [512, 567, 583, 584]. It is an option in all cases, particularly children [585] (LE: 3). The fistula occasionally closes spontaneously. Even in those cases when it does not, the response to a sexual stimulus does allow for intercourse. Androgen deprivation therapy (leuprolide injections, bicalutamide and ketoconazole) has been reported in case series to enable closure of the fistula reducing spontaneous and sleep-related erections [586]. However, sexual dysfunction due to these treatments must be considered.

Blood aspiration is not helpful for the treatment of arterial priapism and the use of α -adrenergic antagonists is not recommended due to potential severe adverse effects, e.g. transfer of the drug into the systemic circulation.

3.4.2.4.1.1 Selective arterial embolisation

Selective arterial embolisation can be performed using either an autologous clot [587-589], gel foam or sponge [588, 590], or more permanent substances, such as coils [588, 590-592] or acrylic glue [593] (LE: 3). Success rates of up to 89% have been reported [594] in relatively small, non-randomised studies. There are no robust data to demonstrate the relative merits of the different substances. At least theoretically, the use of an autologous clot has some attractions. It temporarily seals the fistula, but when the clot is lysed, the arterial damage has usually resolved and the blood flow of the penis can return to normal. The use of a permanent device, such as a coil, would permanently block an artery and may lead to adverse effects upon spontaneous sexual function. Other potential complications include penile gangrene, gluteal ischaemia, cavernositis and perineal abscess [494, 595].

Following percutaneous embolisation, a follow-up is appropriate within one to two weeks. Assessment by clinical examination and by colour duplex US can determine whether the embolisation has been successful [511]. If there is doubt, a repeat arteriogram is required. Recurrence rates of 7-27% after a single treatment with embolisation have been reported [588, 589, 596] (LE: 3). In a few cases, repeat embolisation is necessary. Sexual function following embolisation can be adversely affected although there is full restoration of potency in around 80% of men [596, 597] (LE: 3).

Embolisation in children, although reportedly successful, is technically challenging and requires treatment within a specialist paediatric vascular radiology department [520, 598].

3.4.2.4.2 Surgical management

Selective ligation of the fistula through a transcorporeal approach under the guidance of colour duplex US is possible [4, 509, 599]. Surgery is technically challenging and may pose significant risks, mainly ED due to accidental ligation of the cavernous artery instead of the fistula. It is rarely performed and should only be considered when there are contraindications for selective embolisation, no availability of the technique or embolisation failure (LE: 4).

3.4.2.4.3 Summary of evidence and recommendations for the treatment of arterial priapism

Summary of evidence	LE
Because high-flow priapism is not an emergency, perform definitive management at the discretion of the treating physician.	2b
Conservative management with the use of ice applied to the perineum or site-specific perineal compression may be successful particularly in children. The use of androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	3
Artery embolisation, using temporary or permanent substances, has high success rates. No definitive statement can be made on the best substance for embolisation in terms of sexual function preservation.	3
Repeat the procedure for the recurrence of arterial priapism following selective artery embolisation.	2b
Reserve selective surgical ligation of the fistula as a last treatment option when embolisation has failed.	3

Recommendations	GR
Because high-flow priapism is not an emergency, perform definitive management at the discretion of the treating physician.	B
Manage conservatively with the use of ice applied to the perineum or site-specific perineal compression as the first step, especially in children. Use androgen deprivation therapy only in adults.	C
Perform selective artery embolisation, using temporary or permanent substances.	B
Repeat the procedure for the recurrence of arterial priapism following selective artery embolisation.	B
Reserve selective surgical ligation of the fistula as a final treatment option when embolisation has failed.	C

3.4.2.4.4 Follow-up

Follow-up after successful treatment of arterial priapism should include assessment of erectile function and clinical examination to identify signs of recurrence especially after embolisation.

3.4.3 **Stuttering (recurrent or intermittent) priapism**

3.4.3.1 *Epidemiology/aetiology/pathophysiology*

Robust epidemiological studies of stuttering priapism are lacking [8, 600]. However, recurrent priapism episodes are common in men with sickle cell disease (42-64%) [601, 602] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [8].

The aetiology of stuttering priapism is similar to that of ischaemic priapism. While sickle cell disease is the most common cause, idiopathic cases and cases due to a neurological disorder have been reported. Moreover, men who have suffered from an acute ischaemic priapic event, especially one which has been prolonged (more than four hours) are at risk for developing stuttering priapism [564].

Recently, several studies have proposed alternative mechanisms including inflammation, cellular adhesion, NO metabolism, vascular reactivity and coagulation [494, 504, 532, 603, 604].

3.4.3.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of stuttering priapism

Summary of evidence	LE
Stuttering priapism is similar to ischaemic priapism in that it is low-flow, ischaemic and, if left untreated would result in significant penile damage, with sickle cell disease being the most common cause. But the cause can also be idiopathic and in rare cases may be due to a neurological disorder.	3

3.4.3.2 Classification

Stuttering priapism, also termed intermittent or recurrent priapism, is a distinct condition that is characterised by repetitive and painful episodes of prolonged erections. Erections are self-limited with intervening periods of detumescence [532, 603]. These are analogous to repeated episodes of low-flow (or ischaemic) priapism. The duration of the erectile episodes is generally shorter than in ischaemic priapism [4]. The frequency and/or duration of these episodes is variable and a single episode can sometimes progress into a major ischaemic priapic episode.

3.4.3.3 Diagnostic evaluation

3.4.3.3.1 History

A comprehensive history is mandatory and follows the same principles as described in Table 12. There is a history of recurrent episodes of prolonged erections. The onset of the priapic episodes usually occurs during sleep and detumescence does not occur upon waking. Many of these priapic episodes are painful and may be the reason that the patient seeks medical help.

3.4.3.3.2 Physical examination

Erections are painful and the penis is rigid as in ischaemic priapism, but the duration of events is usually shorter. Between erections the penis is usually normal, but in some cases signs of fibrosis can be found. Rarely, the penis may become enlarged, a condition known as megalophallus.

3.4.3.3.3 Laboratory testing

Laboratory testing follows the same principles as in the two other types of priapism. It is recommended to identify possible causes and should be directed by history, clinical and laboratory findings.

3.4.3.3.4 Penile imaging

There are no specific findings for stuttering priapism. Colour duplex US of the penis and perineum and MRI are recommended and can differentiate arterial from ischaemic type of priapism.

3.4.3.3.5 Recommendations for the diagnosis of stuttering priapism

The same recommendations as described in section 3.4.1.3.5 apply. Stuttering priapism is a recurrent or intermittent type of ischaemic priapism.

3.4.3.4 Disease management

The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can usually be achieved pharmacologically. The management of each acute episode is similar to that for ischaemic priapism; aspiration/irrigation in combination with intracavernous injections of α -adrenergic agonists. Unfortunately, the efficacy and safety of the various treatment modalities reported in the medical literature are poorly characterised. Specifically, most reports are from small case series and the Panel is not aware of any published, well-designed, controlled studies on the efficacy and safety of these treatments [503, 532, 603].

3.4.3.4.1 α -adrenergic agonists

Studies of oral α -adrenergic agonists have suggested some benefit for daily dosing of these agents as effective prevention [605]. Side-effects include tachycardia and palpitations. Pseudoephedrine, widely used as an oral decongestant, can also be used as a first-line treatment [529]. However, its effect on corporal smooth muscle is not fully understood. Etilephrine has been used successfully to prevent stuttering priapism due to sickle cell anaemia. It is taken orally at doses of 50-100 mg daily, with response rates of up to 72% [11, 606, 607]. In one randomised, placebo-controlled, clinical study looking at medical prophylaxis with etilephrine and ephedrine, there was no difference in efficacy between the two drugs.

3.4.3.4.2 Hormonal manipulations of circulating testosterone

The aim of hormonal manipulation is to down-regulate circulating testosterone levels to suppress the action of androgens on penile erection [503, 532, 608]. This can be done through the use of GnRH agonists or antagonists, antiandrogens or oestrogens [609] (LE: 4). Potential side-effects may include hot flushes, gynaecomastia, impaired erectile function, loss of libido and asthenia. All approaches have a similar efficacy profile (LE: 4) while the potential cardiovascular toxicity of oestrogens limits their clinical use. Alternative endocrine approaches that have been used with some success include 5- α -reductase inhibitors [610] (LE: 3) and ketoconazole, an antifungal agent that reduces adrenal and testicular androgen production [608, 611] (LE: 4).

Of the hormonal agents suggested for preventing priapism, GnRH agonists and anti-androgens appear to be the most efficacious and safe. They are recommended as primary treatments for the management of stuttering priapism in adult men (LE: 4).

The duration of hormonal treatment for effective suppression of recurrent priapic events is problematic. It is not possible to make any conclusions on the efficacy, dose and the duration of treatment. Moreover, hormonal agents have a contraceptive effect and interfere with normal sexual maturation. Caution is therefore strongly advised when prescribing hormonal treatments to pre-pubertal boys, adolescents or men who are trying with their female partner to conceive. Castrate levels of testosterone, which have a contraceptive effect, interfere with growth, and significantly affect sexual function.

3.4.3.4.3 Digoxin

Digoxin (a cardiac glycoside and a positive inotrope) is used to treat patients with congestive heart failure. Digoxin regulates smooth muscle tone through a number of different pathways leading to penile detumescence [503, 532, 612]. The use of maintenance digoxin doses (0.25-0.5 mg daily) in idiopathic stuttering priapism has been proven to reduce the number of hospital visits and to improve QoL [532]. A small, clinical, double-blind, placebo-controlled study, using digoxin, produced a decrease in sexual desire and excitement with a concomitant reduction in penile rigidity, regardless of any significant change in plasma levels of testosterone, oestrogens and luteinising hormone [612] (LE: 2b). Side-effects may include a decreased libido, anorexia, nausea, vomiting, confusion, blurred vision, headache, gynaecomastia, rash and arrhythmia.

3.4.3.4.4 Terbutaline

Terbutaline is a β -agonist that causes vasodilation, resulting in smooth muscle relaxation of the vasculature [503, 532] and has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [529] (LE: 3). The only randomised, placebo-controlled study ($n = 68$) in patients with pharmacologically-induced priapism, showed detumescence in 42% of the terbutaline-treated group compared to only 15% in the placebo-treated group [530] (LE: 1b). Side-effects include nervousness, shakiness, drowsiness, heart palpitations, headache, dizziness, hot flashes, nausea and weakness.

3.4.3.4.5 Gabapentin

Gabapentin has anticonvulsant, antinociceptive and anxiolytic properties and is widely used as an analgesic and antiepileptic agent. Its proposed mechanism of action is to inhibit voltage-gated calcium channels, which attenuates synaptic transmission [608], and reduces testosterone- and FSH levels [613]. It is given at a dose of 400 mg, four times a day, up to 2,400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of gabapentin, 300 mg daily [614] (LE: 4). Side-effects include anorgasmia and impaired erectile function.

3.4.3.4.6 Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) derivative that acts as a muscle relaxant and anti-muscle spasm agent. It can inhibit penile erection and ejaculation through GABA activity and prevents recurrent reflexogenic erections or prolonged erections from neurological diseases [503]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal baclofen dosing is more effective [532, 615-617] (LE: 4). Side-effects include drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension and nausea.

3.4.3.4.7 Hydroxyurea

Hydroxyurea blocks the synthesis of deoxyribonucleic acid (DNA) by inhibiting ribonucleotide reductase, which has the effect of arresting cells in the S-phase [608, 618]. It is an established treatment for ameliorating sickle cell disease and improving patient life expectancy [531, 619]. For such patients with recurrent priapism there is limited evidence to suggest a medical prophylactic role (LE: 3), [608, 618, 620]. Side-effects include oligozoospermia and leg ulcers.

3.4.3.4.8 Phosphodiesterase type 5 inhibitors

Low doses of PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism [503, 532, 621-625] (LE: 3). It is important to remember that therapy should be started when the penis is in its flaccid state and not during an acute episode. There is a delay of one week before treatment is effective. There are no reported impairments in male sexual function (LE: 3). Phosphodiesterase type 5 inhibitors probably act in priapism by increasing the concentration of cGMP in the smooth muscle in a NO dysfunctional state. This can occur in priapism and may result in a change in the NO pathway, with down-regulation of cavernosal PDE5 thereby preventing the complete degradation of cGMP in the corpora cavernosa [503, 532, 621, 624].

3.4.3.4.9 Intracavernosal injections

Some patients with stuttering priapism, who have been started on systemic treatments to prevent recurrence of unwanted erections, may not see therapeutic benefits immediately and may temporarily require intracavernous self-injections at home with sympathomimetic agents [503, 532]. The most commonly used drugs are phenylephrine and etilephrine (as described in the treatment of ischaemic priapism) [4, 494, 600, 607] (LE: 3). Side-effects include hypertension, coronary ischaemia and cardiac arrhythmias.

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the pro-enzyme plasminogen to plasmin, which acts as a fibrinolytic enzyme. Limited clinical data have suggested that a single intracavernous injection of TPA can successfully treat patients with recalcitrant priapism [608, 626] (LE: 3). Mild bleeding is the most commonly observed side-effect.

3.4.3.4.10 Summary of evidence and recommendations for the treatment of stuttering priapism

Summary of evidence	LE
The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can generally be achieved pharmacologically.	2b
PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease associated priapism.	3
The evidence with other systemic drugs (digoxin, α -adrenergic agonists, baclofen, gabapentin, terbutaline) is very limited.	3

Recommendations	GR
Manage each acute episode similar to that for ischaemic priapism.	B
Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or antiandrogens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached.	C
Initiate treatment with phosphodiesterase type 5 inhibitors (PDE5Is) only when the penis is in its flaccid state.	C
Use digoxin, α -adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with very frequent and uncontrolled relapses.	C
Use intracavernous self-injections at home of sympathomimetic drugs for the treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	C

3.4.3.5 Follow-up

Follow-up for stuttering priapism include history and clinical examination to assess the efficacy of treatments in preventing or alleviating erectile events as well as assessing erectile function and penile fibrosis.

4. REFERENCES

1. Lindau, S.T., *et al.* A study of sexuality and health among older adults in the United States. *N Engl J Med*, 2007. 357: 762.
<https://www.ncbi.nlm.nih.gov/pubmed/17715410>
2. Rosenberg, M.T., *et al.* Identification and diagnosis of premature ejaculation. *Int J Clin Pract*, 2007. 61: 903.
<https://www.ncbi.nlm.nih.gov/pubmed/17504352>
3. Tekgül, S., *et al.* European Association of Urology guidelines on Paediatric Urology. Edn. presented at the EAU Annual Congress Munich. 2016.
4. Montague, D.K., *et al.* American Urological Association guideline on the management of priapism. *J Urol*, 2003. 170: 1318.
<https://www.ncbi.nlm.nih.gov/pubmed/14501756>
5. Eland, I.A., *et al.* Incidence of priapism in the general population. *Urology*, 2001. 57: 970.
<https://www.ncbi.nlm.nih.gov/pubmed/11337305>
6. Kulmala, R.V., *et al.* Priapism, its incidence and seasonal distribution in Finland. *Scand J Urol Nephrol*, 1995. 29: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/7618054>
7. Furtado, P.S., *et al.* The prevalence of priapism in children and adolescents with sickle cell disease in Brazil. *Int J Hematol*, 2012. 95: 648.
<https://www.ncbi.nlm.nih.gov/pubmed/22539365>
8. Adeyolu, A.B., *et al.* Priapism in sickle-cell disease; incidence, risk factors and complications - an international multicentre study. *BJU Int*, 2002. 90: 898.
<https://www.ncbi.nlm.nih.gov/pubmed/12460353>
9. Emond, A.M., *et al.* Priapism and impotence in homozygous sickle cell disease. *Arch Intern Med*, 1980. 140: 1434.
<https://www.ncbi.nlm.nih.gov/pubmed/6159833>
10. Lionnet, F., *et al.* Hemoglobin sickle cell disease complications: a clinical study of 179 cases. *Haematologica*, 2012. 97: 1136.
<https://www.ncbi.nlm.nih.gov/pubmed/22315500>
11. Olujhungbe, A.B., *et al.* A prospective diary study of stuttering priapism in adolescents and young men with sickle cell anemia: report of an international randomized control trial--the priapism in sickle cell study. *J Androl*, 2011. 32: 375.
<https://www.ncbi.nlm.nih.gov/pubmed/21127308>
12. Wespes, E., *et al.*, EAU Guidelines Panel on Male Sexual Dysfunction. EAU Guidelines on Male Sexual Dysfunction (Erectile Dysfunction and premature ejaculation). Edn. presented at the EAU Annual congress Stockholm. 2009: Arnhem, The Netherlands.
<http://uroweb.org/guideline/male-sexual-dysfunction/>
13. Hatzimouratidis, K., *et al.*, EAU Guidelines Panel on Male Sexual Dysfunction. EAU guidelines on Penile Curvature. Edn. presented at the EAU Annual Congress Paris. 2012: Arnhem, The Netherlands.
<http://uroweb.org/guideline/penile-curvature/>
14. Salonia, A., *et al.*, EAU Guidelines Panel on Male Sexual Dysfunction. EAU guidelines on priapism. Edn. presented at the EAU Annual Congress Stockholm. 2014: Arnhem, The Netherlands
<http://uroweb.org/guideline/priapism/>
15. Hatzimouratidis, K., *et al.*, EAU Guidelines Panel on Male Sexual Dysfunction. EAU guidelines on Male Sexual Dysfunction. Edn. presented at the EAU Annual Congress Munich 2016.
<http://uroweb.org/guideline/male-sexual-dysfunction/>
16. Hatzimouratidis, K., *et al.* Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol*, 2010. 57: 804.
<https://www.ncbi.nlm.nih.gov/pubmed/>
17. Hatzimouratidis, K., *et al.* EAU guidelines on penile curvature. *Eur Urol*, 2012. 62: 543.
<https://www.ncbi.nlm.nih.gov/pubmed/22658761>
18. Salonia, A., *et al.* European Association of Urology guidelines on priapism. *Eur Urol*, 2014. 65: 480.
<https://www.ncbi.nlm.nih.gov/pubmed/24314827>
19. Wespes, E., *et al.* EAU Guidelines on erectile dysfunction: an update. *Eur Urol*, 2006. 49: 806.
<https://www.ncbi.nlm.nih.gov/pubmed/>
20. Wespes, E., *et al.* Guidelines on erectile dysfunction. *Eur Urol*, 2002. 41: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/>

21. Phillips, B. Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
22. Van den Broeck, T. *et al.* What are the benefits and harms of testosterone treatment for male sexual dysfunction? PROSPERO: International prospective register of systematic reviews, 2015.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015028029
23. Gratzke, C., *et al.* Anatomy, physiology, and pathophysiology of erectile dysfunction. *J Sex Med*, 2010. 7: 445.
<https://www.ncbi.nlm.nih.gov/pubmed/20092448>
24. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA*, 1993. 270: 83.
<https://www.ncbi.nlm.nih.gov/pubmed/8510302>
25. Feldman, H.A., *et al.* Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*, 1994. 151: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/8254833>
26. Fisher, W.A., *et al.* Erectile dysfunction (ED) is a shared sexual concern of couples I: couple conceptions of ED. *J Sex Med*, 2009. 6: 2746.
<https://www.ncbi.nlm.nih.gov/pubmed/19694926>
27. Salonia, A., *et al.* Is erectile dysfunction a reliable proxy of general male health status? The case for the International Index of Erectile Function-Erectile Function domain. *J Sex Med*, 2012. 9: 2708.
<https://www.ncbi.nlm.nih.gov/pubmed/22897643>
28. Dong, J.Y., *et al.* Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. *J Am Coll Cardiol*, 2011. 58: 1378.
<https://www.ncbi.nlm.nih.gov/pubmed/21920268>
29. Gandaglia, G., *et al.* A systematic review of the association between erectile dysfunction and cardiovascular disease. *Eur Urol*, 2014. 65: 968.
<https://www.ncbi.nlm.nih.gov/pubmed/24011423>
30. Gupta, B.P., *et al.* The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med*, 2011. 171: 1797.
<https://www.ncbi.nlm.nih.gov/pubmed/21911624>
31. Braun, M., *et al.* Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *Int J Impot Res*, 2000. 12: 305.
<https://www.ncbi.nlm.nih.gov/pubmed/11416833>
32. Johannes, C.B., *et al.* Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *J Urol*, 2000. 163: 460.
<https://www.ncbi.nlm.nih.gov/pubmed/10647654>
33. Schouten, B.W., *et al.* Incidence rates of erectile dysfunction in the Dutch general population. Effects of definition, clinical relevance and duration of follow-up in the Krimpen Study. *Int J Impot Res*, 2005. 17: 58.
<https://www.ncbi.nlm.nih.gov/pubmed/15510192>
34. Capogrosso, P., *et al.* One patient out of four with newly diagnosed erectile dysfunction is a young man--worrisome picture from the everyday clinical practice. *J Sex Med*, 2013. 10: 1833.
<https://www.ncbi.nlm.nih.gov/pubmed/23651423>
35. Buvat, J., *et al.* Endocrine aspects of male sexual dysfunctions. *J Sex Med*, 2010. 7: 1627.
<https://www.ncbi.nlm.nih.gov/pubmed/20388162>
36. Jackson, G., *et al.* Cardiovascular aspects of sexual medicine. *J Sex Med*, 2010. 7: 1608.
<https://www.ncbi.nlm.nih.gov/pubmed/20388161>
37. Besiroglu, H., *et al.* The relationship between metabolic syndrome, its components, and erectile dysfunction: a systematic review and a meta-analysis of observational studies. *J Sex Med*, 2015. 12: 1309.
<https://www.ncbi.nlm.nih.gov/pubmed/25872648>
38. Binmoammar, T.A., *et al.* The impact of poor glycaemic control on the prevalence of erectile dysfunction in men with type 2 diabetes mellitus: a systematic review. *JRSM Open*, 2016. 7: 2054270415622602.
<https://www.ncbi.nlm.nih.gov/pubmed/26981254>
39. Glina, S., *et al.* Modifying risk factors to prevent and treat erectile dysfunction. *J Sex Med*, 2013. 10: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/22971247>

40. Vlachopoulos, C., *et al.* Erectile dysfunction in the cardiovascular patient. *Eur Heart J*, 2013. 34: 2034.
<https://www.ncbi.nlm.nih.gov/pubmed/23616415>
41. Seftel, A.D., *et al.* Coexisting lower urinary tract symptoms and erectile dysfunction: a systematic review of epidemiological data. *Int J Clin Pract*, 2013. 67: 32.
<https://www.ncbi.nlm.nih.gov/pubmed/23082930>
42. Rosen, R., *et al.* Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol*, 2003. 44: 637.
<https://www.ncbi.nlm.nih.gov/pubmed/14644114>
43. Molina Leyva, A., *et al.* Sexual dysfunction in psoriasis: a systematic review. *J Eur Acad Dermatol Venereol*, 2015. 29: 649.
<https://www.ncbi.nlm.nih.gov/pubmed/25424331>
44. Fan, D., *et al.* Male sexual dysfunction and ankylosing spondylitis: a systematic review and metaanalysis. *J Rheumatol*, 2015. 42: 252.
<https://www.ncbi.nlm.nih.gov/pubmed/25448789>
45. Duman, D.G., *et al.* Nonalcoholic Fatty Liver Disease is Associated with Erectile Dysfunction: A Prospective Pilot Study. *J Sex Med*, 2016. 13: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/26853046>
46. Murray, K.S., *et al.* - A prospective study of erectile function after transrectal ultrasonography-guided prostate biopsy. *BJU Int*, 2015. 116: 190.
<https://www.ncbi.nlm.nih.gov/pubmed/25430505>
47. Mottet, N., *et al.* EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27568654>
48. Salonia, A., *et al.* Prevention and management of postprostatectomy sexual dysfunctions part 2: recovery and preservation of erectile function, sexual desire, and orgasmic function. *Eur Urol*, 2012. 62: 273.
<https://www.ncbi.nlm.nih.gov/pubmed/22575910>
49. Salonia, A., *et al.* Prevention and management of postprostatectomy sexual dysfunctions. Part 1: choosing the right patient at the right time for the right surgery. *Eur Urol*, 2012. 62: 261.
<https://www.ncbi.nlm.nih.gov/pubmed/22575909>
50. Sanda, M.G., *et al.* Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*, 2008. 358: 1250.
<https://www.ncbi.nlm.nih.gov/pubmed/18354103>
51. Schauer, I., *et al.* Have rates of erectile dysfunction improved within the past 17 years after radical prostatectomy? A systematic analysis of the control arms of prospective randomized trials on penile rehabilitation. *Andrology*, 2015. 3: 661.
<https://www.ncbi.nlm.nih.gov/pubmed/26198796>
52. Ficarra, V., *et al.* Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. *Eur Urol*, 2012. 62: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/22749850>
53. Stolzenburg, J.U., *et al.* Effect of surgical approach on erectile function recovery following bilateral nerve-sparing radical prostatectomy: An evaluation utilising data from a randomised, double-blind, double-dummy multicentre trial of tadalafil vs placebo. *BJU Int*, 2015. 116: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/25560809>
54. Haglind, E., *et al.* Urinary Incontinence and Erectile Dysfunction after Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. *Eur Urol*, 2015. 68: 216.
<https://www.ncbi.nlm.nih.gov/pubmed/25770484>
55. Yaxley, J.W., *et al.* Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet*, 2016. 388: 1057.
<https://www.ncbi.nlm.nih.gov/pubmed/27474375>
56. Isgoren, A., *et al.* Erectile function outcomes after robot-assisted radical prostatectomy: is it superior to open retropubic or laparoscopic approach? *Sex Med Rev*, 2014. 2.
<https://www.ncbi.nlm.nih.gov/pubmed/27784540>
57. Glickman, L., *et al.* Changes in continence and erectile function between 2 and 4 years after radical prostatectomy. *J Urol*, 2009. 181: 731.
<https://www.ncbi.nlm.nih.gov/pubmed/19091349>

58. Incrocci, L., *et al.* Pelvic radiotherapy and sexual function in men and women. *J Sex Med*, 2013. 10 Suppl 1: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/23387912>
59. Stember, D.S., *et al.* The concept of erectile function preservation (penile rehabilitation) in the patient after brachytherapy for prostate cancer. *Brachytherapy*, 2012. 11: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/22330103>
60. Cordeiro, E.R., *et al.* High-intensity focused ultrasound (HIFU) for definitive treatment of prostate cancer. *BJU Int*, 2012. 110: 1228.
<https://www.ncbi.nlm.nih.gov/pubmed/22672199>
61. Williams, S.B., *et al.* Comparative effectiveness of cryotherapy vs brachytherapy for localised prostate cancer. *BJU Int*, 2012. 110: E92.
<https://www.ncbi.nlm.nih.gov/pubmed/22192688>
62. Hatzichristou, D., *et al.* Diagnosing Sexual Dysfunction in Men and Women: Sexual History Taking and the Role of Symptom Scales and Questionnaires. *J Sex Med*, 2016. 13: 1166.
<https://www.ncbi.nlm.nih.gov/pubmed/27436074>
63. The process of care model for evaluation and treatment of erectile dysfunction. The Process of Care Consensus Panel. *Int J Impot Res*, 1999. 11: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/10356665>
64. Althof, S.E., *et al.* Standard operating procedures for taking a sexual history. *J Sex Med*, 2013. 10: 26.
<https://www.ncbi.nlm.nih.gov/pubmed/22970717>
65. Rosen, R.C., *et al.* The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*, 1997. 49: 822.
<https://www.ncbi.nlm.nih.gov/pubmed/9187685>
66. Rosen, R.C., *et al.* Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res*, 1999. 11: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/10637462>
67. Mulhall, J.P., *et al.* Validation of the erection hardness score. *J Sex Med*, 2007. 4: 1626.
<https://www.ncbi.nlm.nih.gov/pubmed/17888069>
68. Whooley, M.A., *et al.* Case-finding instruments for depression. Two questions are as good as many. *J Gen Intern Med*, 1997. 12: 439.
<https://www.ncbi.nlm.nih.gov/pubmed/9229283>
69. Khera, M., *et al.* Diagnosis and Treatment of Testosterone Deficiency: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015). *J Sex Med*, 2016. 13: 1787.
<https://www.ncbi.nlm.nih.gov/pubmed/27914560>
70. Davis-Joseph, B., *et al.* Accuracy of the initial history and physical examination to establish the etiology of erectile dysfunction. *Urology*, 1995. 45: 498.
<https://www.ncbi.nlm.nih.gov/pubmed/7879338>
71. Ghanem, H.M., *et al.* SOP: physical examination and laboratory testing for men with erectile dysfunction. *J Sex Med*, 2013. 10: 108.
<https://www.ncbi.nlm.nih.gov/pubmed/23343170>
72. Bhasin, S., *et al.* Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, 2010. 95: 2536.
<https://www.ncbi.nlm.nih.gov/pubmed/20525905>
73. Isidori, A.M., *et al.* A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment—a systematic review. *Eur Urol*, 2014. 65: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/24050791>
74. O'Connor, D.B., *et al.* The relationships between sex hormones and sexual function in middle-aged and older European men. *J Clin Endocrinol Metab*, 2011. 96: E1577.
<https://www.ncbi.nlm.nih.gov/pubmed/21849522>
75. Heidenreich, A., *et al.* EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent—update 2013. *Eur Urol*, 2014. 65: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/24207135>
76. Maggi, M., *et al.* Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA). *J Sex Med*, 2013. 10: 661.
<https://www.ncbi.nlm.nih.gov/pubmed/22524444>
77. Laumann, E.O., *et al.* The epidemiology of erectile dysfunction: results from the National Health and Social Life Survey. *Int J Impot Res*, 1999. 11 Suppl 1: S60.
<https://www.ncbi.nlm.nih.gov/pubmed/10554933>

78. Miner, M., *et al.* Cardiometabolic risk and female sexual health: the Princeton III summary. *J Sex Med*, 2012. 9: 641.
<https://www.ncbi.nlm.nih.gov/pubmed/22372651>
79. Gazzaruso, C., *et al.* Erectile dysfunction can improve the effectiveness of the current guidelines for the screening for asymptomatic coronary artery disease in diabetes. *Endocrine*, 2011. 40: 273.
<https://www.ncbi.nlm.nih.gov/pubmed/21861245>
80. Turek, S.J., *et al.* Sexual dysfunction as a marker of cardiovascular disease in males with 50 or more years of type 1 diabetes. *Diabetes Care*, 2013. 36: 3222.
<https://www.ncbi.nlm.nih.gov/pubmed/23780949>
81. Vlachopoulos, C., *et al.* Prediction of cardiovascular events with aortic stiffness in patients with erectile dysfunction. *Hypertension*, 2014. 64: 672.
<https://www.ncbi.nlm.nih.gov/pubmed/24980671>
82. Fang, S.C., *et al.* Changes in erectile dysfunction over time in relation to Framingham cardiovascular risk in the Boston Area Community Health (BACH) Survey. *J Sex Med*, 2015. 12: 100.
<https://www.ncbi.nlm.nih.gov/pubmed/25293632>
83. Nehra, A., *et al.* The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc*, 2012. 87: 766.
<https://www.ncbi.nlm.nih.gov/pubmed/22862865>
84. DeBusk, R., *et al.* Management of sexual dysfunction in patients with cardiovascular disease: recommendations of The Princeton Consensus Panel. *Am J Cardiol*, 2000. 86: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/10913479>
85. Kostis, J.B., *et al.* Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol*, 2005. 96: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/16018863>
86. Hatzichristou, D.G., *et al.* Nocturnal penile tumescence and rigidity monitoring in young potent volunteers: reproducibility, evaluation criteria and the effect of sexual intercourse. *J Urol*, 1998. 159: 1921.
<https://www.ncbi.nlm.nih.gov/pubmed/9598488>
87. Hatzichristou, D.G., *et al.* Hemodynamic characterization of a functional erection. Arterial and corporeal veno-occlusive function in patients with a positive intracavernosal injection test. *Eur Urol*, 1999. 36: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/10364657>
88. Sikka, S.C., *et al.* Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. *J Sex Med*, 2013. 10: 120.
<https://www.ncbi.nlm.nih.gov/pubmed/22970798>
89. Glina, S., *et al.* SOP: corpus cavernosum assessment (cavernosography/cavernosometry). *J Sex Med*, 2013. 10: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/22971225>
90. Montorsi, F., *et al.* Summary of the recommendations on sexual dysfunctions in men. *J Sex Med*, 2010. 7: 3572.
<https://www.ncbi.nlm.nih.gov/pubmed/16422979>
91. Hatzichristou, D., *et al.* Recommendations for the clinical evaluation of men and women with sexual dysfunction. *J Sex Med*, 2010. 7: 337.
<https://www.ncbi.nlm.nih.gov/pubmed/20092443>
92. Hatzimouratidis, K., *et al.* Pharmacotherapy for Erectile Dysfunction: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015). *J Sex Med*, 2016. 13: 465.
<https://www.ncbi.nlm.nih.gov/pubmed/27045254>
93. Moyad, M.A., *et al.* Prevention and treatment of erectile dysfunction using lifestyle changes and dietary supplements: what works and what is worthless, part II. *Urol Clin North Am*, 2004. 31: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/15123406>
94. Montorsi, F., *et al.* Efficacy of sildenafil citrate in men with erectile dysfunction following radical prostatectomy: a systematic review of clinical data. *J Sex Med*, 2005. 2: 658.
<https://www.ncbi.nlm.nih.gov/pubmed/16422824>
95. Schwartz, E.J., *et al.* Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. *J Urol*, 2004. 171: 771.
<https://www.ncbi.nlm.nih.gov/pubmed/14713808>
96. Padma-Nathan, H., *et al.* Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. *Int J Impot Res*, 2008. 20: 479.
<https://www.ncbi.nlm.nih.gov/pubmed/18650827>

97. Kim, D.J., *et al.* A prospective, randomized, placebo-controlled trial of on-Demand vs. nightly sildenafil citrate as assessed by Rigiscan and the international index of erectile function. *Andrology*, 2016. 4: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/26663669>
98. Montorsi, F., *et al.* Tadalafil in the treatment of erectile dysfunction following bilateral nerve sparing radical retropubic prostatectomy: a randomized, double-blind, placebo controlled trial. *J Urol*, 2004. 172: 1036.
<https://www.ncbi.nlm.nih.gov/pubmed/15311032>
99. Brock, G., *et al.* Safety and efficacy of vardenafil for the treatment of men with erectile dysfunction after radical retropubic prostatectomy. *J Urol*, 2003. 170: 1278.
<https://www.ncbi.nlm.nih.gov/pubmed/14501741>
100. Nehra, A., *et al.* Vardenafil improved patient satisfaction with erectile hardness, orgasmic function and sexual experience in men with erectile dysfunction following nerve sparing radical prostatectomy. *J Urol*, 2005. 173: 2067.
<https://www.ncbi.nlm.nih.gov/pubmed/15879836>
101. Montorsi, F., *et al.* Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). *Eur Urol*, 2014. 65: 587.
<https://www.ncbi.nlm.nih.gov/pubmed/24169081>
102. Moncada, I., *et al.* Effects of tadalafil once daily or on demand versus placebo on time to recovery of erectile function in patients after bilateral nerve-sparing radical prostatectomy. *World J Urol*, 2015. 33: 1031.
<https://www.ncbi.nlm.nih.gov/pubmed/25155034>
103. Patel, H.R., *et al.* Effects of tadalafil treatment after bilateral nerve-sparing radical prostatectomy: quality of life, psychosocial outcomes, and treatment satisfaction results from a randomized, placebo-controlled phase IV study. *BMC Urol*, 2015. 15: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/25879460>
104. Montorsi, F., *et al.* Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. *Eur Urol*, 2008. 54: 924.
<https://www.ncbi.nlm.nih.gov/pubmed/18640769>
105. Mulhall, J.P., *et al.* A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. *J Urol*, 2013. 189: 2229.
<https://www.ncbi.nlm.nih.gov/pubmed/23219537>
106. Corona, G., *et al.* The safety and efficacy of Avanafil, a new 2(nd) generation PDE5i: comprehensive review and meta-analysis. *Expert Opin Drug Saf*, 2016. 15: 237.
<https://www.ncbi.nlm.nih.gov/pubmed/26646748>
107. Cui, H., *et al.* Efficacy and safety of long-term tadalafil 5 mg once daily combined with sildenafil 50 mg as needed at the early stage of treatment for patients with erectile dysfunction. *Andrologia*, 2015. 47: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/24387078>
108. Montorsi, F., *et al.* Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. *J Urol*, 1997. 158: 1408.
<https://www.ncbi.nlm.nih.gov/pubmed/9302132>
109. Raina, R., *et al.* The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. *BJU Int*, 2007. 100: 1317.
<https://www.ncbi.nlm.nih.gov/pubmed/17850385>
110. Raina, R., *et al.* Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. *Int J Impot Res*, 2006. 18: 77.
<https://www.ncbi.nlm.nih.gov/pubmed/16107868>
111. Hellstrom, W.J., *et al.* Implants, mechanical devices, and vascular surgery for erectile dysfunction. *J Sex Med*, 2010. 7: 501.
<https://www.ncbi.nlm.nih.gov/pubmed/20092450>
112. Tal, R., *et al.* Penile implant utilization following treatment for prostate cancer: analysis of the SEER-Medicare database. *J Sex Med*, 2011. 8: 1797.
<https://www.ncbi.nlm.nih.gov/pubmed/21426495>

113. Haahr, M.K., *et al.* Safety and Potential Effect of a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial. *EBioMedicine*, 2016. 5: 204.
<https://www.ncbi.nlm.nih.gov/pubmed/27077129>
114. Tajar, A., *et al.* Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). *J Clin Endocrinol Metab*, 2012. 97: 1508.
<https://www.ncbi.nlm.nih.gov/pubmed/22419720>
115. Lee, J.C., *et al.* Do men with mild erectile dysfunction have the same risk factors as the general erectile dysfunction clinical trial population? *BJU Int*, 2011. 107: 956.
<https://www.ncbi.nlm.nih.gov/pubmed/20950304>
116. Wang, C., *et al.* Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *J Androl*, 2009. 30: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/18772485>
117. Wang, C., *et al.* Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *Eur Urol*, 2009. 55: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/18762364>
118. Khera, M., *et al.* A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol*, 2014. 65: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/24011426>
119. Corona, G., *et al.* Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf*, 2014. 13: 1327.
<https://www.ncbi.nlm.nih.gov/pubmed/25139126>
120. Baillargeon, J., *et al.* Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy. *Ann Pharmacother*, 2014. 48: 1138.
<https://www.ncbi.nlm.nih.gov/pubmed/24989174>
121. Basaria, S., *et al.* Adverse events associated with testosterone administration. *N Engl J Med*, 2010. 363: 109.
<https://www.ncbi.nlm.nih.gov/pubmed/20592293>
122. Calof, O.M., *et al.* Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci*, 2005. 60: 1451.
<https://www.ncbi.nlm.nih.gov/pubmed/16339333>
123. Fernandez-Balsells, M.M., *et al.* Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab*, 2010. 95: 2560.
<https://www.ncbi.nlm.nih.gov/pubmed/20525906>
124. Haddad, R.M., *et al.* Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc*, 2007. 82: 29.
<https://www.ncbi.nlm.nih.gov/pubmed/17285783>
125. Vigen, R., *et al.* Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*, 2013. 310: 1829.
<https://www.ncbi.nlm.nih.gov/pubmed/24193080>
126. Sohn, M., *et al.* Standard operating procedures for vascular surgery in erectile dysfunction: revascularization and venous procedures. *J Sex Med*, 2013. 10: 172.
<https://www.ncbi.nlm.nih.gov/pubmed/23171072>
127. Boddi, V., *et al.* An integrated approach with vardenafil orodispersible tablet and cognitive behavioral sex therapy for treatment of erectile dysfunction: a randomized controlled pilot study. *Andrology*, 2015. 3: 909.
<https://www.ncbi.nlm.nih.gov/pubmed/26311340>
128. Rosen, R.C. Psychogenic erectile dysfunction. Classification and management. *Urol Clin North Am*, 2001. 28: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/11402580>
129. Lue, T.F. Erectile dysfunction. *N Engl J Med*, 2000. 342: 1802.
<https://www.ncbi.nlm.nih.gov/pubmed/10853004>
130. Yuan, J., *et al.* Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. *Eur Urol*, 2013. 63: 902.
<https://www.ncbi.nlm.nih.gov/pubmed/23395275>
131. Goldstein, I., *et al.* Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med*, 1998. 338: 1397.
<https://www.ncbi.nlm.nih.gov/pubmed/9580646>

132. Moncada, I., *et al.* Efficacy of sildenafil citrate at 12 hours after dosing: re-exploring the therapeutic window. *Eur Urol*, 2004. 46: 357.
<https://www.ncbi.nlm.nih.gov/pubmed/15306108>
133. Giuliano, F., *et al.* Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. *Int J Clin Pract*, 2010. 64: 240.
<https://www.ncbi.nlm.nih.gov/pubmed/19900167>
134. Tsertsvadze, A., *et al.* Oral sildenafil citrate (viagra) for erectile dysfunction: a systematic review and meta-analysis of harms. *Urology*, 2009. 74: 831.
<https://www.ncbi.nlm.nih.gov/pubmed/19592078>
135. Goldstein, I., *et al.* Oral sildenafil in the treatment of erectile dysfunction. 1998. *J Urol*, 2002. 167: 1197.
<https://www.ncbi.nlm.nih.gov/pubmed/11905901>
136. Curran, M., *et al.* Tadalafil. *Drugs*, 2003. 63: 2203.
<https://www.ncbi.nlm.nih.gov/pubmed/14498756>
137. Ventimiglia, E., *et al.* The safety of phosphodiesterase type 5 inhibitors for erectile dysfunction. *Expert Opin Drug Saf*, 2016. 15: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/26752541>
138. Chen, L., *et al.* Phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction: A trade-off network meta-analysis. *Eur Urol*, 2015. 68: 674.
<https://www.ncbi.nlm.nih.gov/pubmed/25817916>
139. Keating, G.M., *et al.* Vardenafil: a review of its use in erectile dysfunction. *Drugs*, 2003. 63: 2673.
<https://www.ncbi.nlm.nih.gov/pubmed/14636086>
140. Gacci, M., *et al.* Latest Evidence on the Use of Phosphodiesterase Type 5 Inhibitors for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *Eur Urol*, 2016. 70: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/26806655>
141. Chung, E., *et al.* A state of art review on vardenafil in men with erectile dysfunction and associated underlying diseases. *Expert Opin Pharmacother*, 2011. 12: 1341.
<https://www.ncbi.nlm.nih.gov/pubmed/21548725>
142. Sanford, M. Vardenafil orodispersible tablet. *Drugs*, 2012. 72: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/21548725>
143. Debruyne, F.M., *et al.* Time to onset of action of vardenafil: a retrospective analysis of the pivotal trials for the orodispersible and film-coated tablet formulations. *J Sex Med*, 2011. 8: 2912.
<https://www.ncbi.nlm.nih.gov/pubmed/21883954>
144. Sperling, H., *et al.* The POTENT I randomized trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. *J Sex Med*, 2010. 7: 1497.
<https://www.ncbi.nlm.nih.gov/pubmed/20233275>
145. Gittelman, M., *et al.* The POTENT II randomised trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. *Int J Clin Pract*, 2010. 64: 594.
<https://www.ncbi.nlm.nih.gov/pubmed/20456213>
146. Wang, R., *et al.* Selectivity of avanafil, a PDE5 inhibitor for the treatment of erectile dysfunction: implications for clinical safety and improved tolerability. *J Sex Med*, 2012. 9: 2122.
<https://www.ncbi.nlm.nih.gov/pubmed/22759639>
147. Kyle, J.A., *et al.* Avanafil for erectile dysfunction. *Ann Pharmacother*, 2013. 47: 1312.
<https://www.ncbi.nlm.nih.gov/pubmed/24259695>
148. Goldstein, I., *et al.* A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. *J Sex Med*, 2012. 9: 1122.
<https://www.ncbi.nlm.nih.gov/pubmed/22248153>
149. Hellstrom, W.J., *et al.* Efficacy of Avanafil 15 Minutes after Dosing in Men with Erectile Dysfunction: A Randomized, Double-Blind, Placebo Controlled Study. *J Urol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/25591992>
150. Wang, H., *et al.* The effectiveness and safety of avanafil for erectile dysfunction: a systematic review and meta-analysis. *Curr Med Res Opin*, 2014. 30: 1565.
<https://www.ncbi.nlm.nih.gov/pubmed/24701971>
151. Burns, P.R., *et al.* Treatment satisfaction of men and partners following switch from on-demand phosphodiesterase type 5 inhibitor therapy to tadalafil 5mg once daily. *J Sex Med*, 2015. 12: 720.
<https://www.ncbi.nlm.nih.gov/pubmed/25615445>
152. Behr-Roussel, D., *et al.* Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxations in rats: lack of tachyphylaxis. *Eur Urol*, 2005. 47: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/15582254>

153. Ferrini, M.G., *et al.* Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat. *Urology*, 2006. 68: 429.
<https://www.ncbi.nlm.nih.gov/pubmed/16904479>
154. Ferrini, M.G., *et al.* Long-term continuous treatment with sildenafil ameliorates aging-related erectile dysfunction and the underlying corporal fibrosis in the rat. *Biol Reprod*, 2007. 76: 915.
<https://www.ncbi.nlm.nih.gov/pubmed/17287493>
155. Kovanecz, I., *et al.* Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection. *BJU Int*, 2008. 101: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/17888043>
156. Vignozzi, L., *et al.* Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. *J Sex Med*, 2006. 3: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/16681467>
157. Porst, H., *et al.* Tadalafil once daily in men with erectile dysfunction: an integrated analysis of data obtained from 1913 patients from six randomized, double-blind, placebo-controlled, clinical studies. *Eur Urol*, 2014. 65: 455.
<https://www.ncbi.nlm.nih.gov/pubmed/24119319>
158. Buvat, J., *et al.* Continuation and effectiveness of tadalafil once daily during a 6-month observational study in erectile dysfunction: the EDATE study. *Int J Clin Pract*, 2014. 68: 1087.
<https://www.ncbi.nlm.nih.gov/pubmed/25123817>
159. Alberti, L., *et al.* Erectile dysfunction in heart failure patients: a critical reappraisal. *Andrology*, 2013. 1: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/23339018>
160. Giannetta, E., *et al.* Is chronic inhibition of phosphodiesterase type 5 cardioprotective and safe? A meta-analysis of randomized controlled trials. *BMC Med*, 2014. 12: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/25330139>
161. Jackson, G. Hemodynamic and exercise effects of phosphodiesterase 5 inhibitors. *Am J Cardiol*, 2005. 96: 32m.
<https://www.ncbi.nlm.nih.gov/pubmed/16387564>
162. Swearingen, D., *et al.* Hemodynamic effect of avanafil and glyceryl trinitrate coadministration. *Drugs Context*, 2013. 2013: 212248.
<https://www.ncbi.nlm.nih.gov/pubmed/24432037>
163. Pickering, T.G., *et al.* Sildenafil citrate for erectile dysfunction in men receiving multiple antihypertensive agents: a randomized controlled trial. *Am J Hypertens*, 2004. 17: 1135.
<https://www.ncbi.nlm.nih.gov/pubmed/15607620>
164. Kloner, R.A., *et al.* Interaction between the phosphodiesterase 5 inhibitor, tadalafil and 2 alpha-blockers, doxazosin and tamsulosin in healthy normotensive men. *J Urol*, 2004. 172: 1935.
<https://www.ncbi.nlm.nih.gov/pubmed/15540759>
165. McCullough, A.R., *et al.* Achieving treatment optimization with sildenafil citrate (Viagra) in patients with erectile dysfunction. *Urology*, 2002. 60: 28.
<https://www.ncbi.nlm.nih.gov/pubmed/12414331>
166. Forgue, S.T., *et al.* Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol*, 2006. 61: 280.
<https://www.ncbi.nlm.nih.gov/pubmed/16487221>
167. Nichols, D.J., *et al.* Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol*, 2002. 53 Suppl 1: 5S.
<https://www.ncbi.nlm.nih.gov/pubmed/11879254>
168. Rosen, R.C., *et al.* Determining the earliest time within 30 minutes to erectogenic effect after tadalafil 10 and 20 mg: a multicenter, randomized, double-blind, placebo-controlled, at-home study. *J Sex Med*, 2004. 1: 193.
<https://www.ncbi.nlm.nih.gov/pubmed/16422974>
169. Montorsi, F., *et al.* Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind, placebo-controlled trial. *J Sex Med*, 2004. 1: 168.
<https://www.ncbi.nlm.nih.gov/pubmed/16422971>
170. Padma-Nathan, H., *et al.* Minimal time to successful intercourse after sildenafil citrate: results of a randomized, double-blind, placebo-controlled trial. *Urology*, 2003. 62: 400.
<https://www.ncbi.nlm.nih.gov/pubmed/12946731>

171. Rajagopalan, P., *et al.* Effect of high-fat breakfast and moderate-fat evening meal on the pharmacokinetics of vardenafil, an oral phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction. *J Clin Pharmacol*, 2003. 43: 260.
<https://www.ncbi.nlm.nih.gov/pubmed/12638394>
172. Gruenwald, I., *et al.* Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil. *Eur Urol*, 2006. 50: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/16527391>
173. Hatzichristou, D., *et al.* Sildenafil failures may be due to inadequate patient instructions and follow-up: a study on 100 non-responders. *Eur Urol*, 2005. 47: 518.
<https://www.ncbi.nlm.nih.gov/pubmed/16564127>
174. Hatzimouratidis, K., *et al.* Treatment strategy for “non-responders” to tadalafil and vardenafil: a real-life study. *Eur Urol*, 2006. 50: 126.
<https://www.ncbi.nlm.nih.gov/pubmed/16564127>
175. Park, N.C., *et al.* Treatment Strategy for Non-Responders to PDE5 Inhibitors. *World J Mens Health*, 2013. 31: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/23658863>
176. Porst, H., *et al.* SOP conservative (medical and mechanical) treatment of erectile dysfunction. *J Sex Med*, 2013. 10: 130.
<https://www.ncbi.nlm.nih.gov/pubmed/23343170>
177. Marchal Escalona, C., *et al.* PDE5A Polymorphisms Influence on Sildenafil Treatment Success. *J Sex Med*, 2016. 13: 1104.
<https://www.ncbi.nlm.nih.gov/pubmed/27235284>
178. Yuan, J.Q., *et al.* A meta-regression evaluating the effectiveness and prognostic factors of oral phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. *Asian J Androl*, 2016. 18: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/25966626>
179. Greco, E.A., *et al.* Combining testosterone and PDE5 inhibitors in erectile dysfunction: basic rationale and clinical evidences. *Eur Urol*, 2006. 50: 940.
<https://www.ncbi.nlm.nih.gov/pubmed/16979814>
180. Spitzer, M., *et al.* The effect of testosterone on mood and well-being in men with erectile dysfunction in a randomized, placebo-controlled trial. *Andrology*, 2013. 1: 475.
<https://www.ncbi.nlm.nih.gov/pubmed/23494931>
181. Spitzer, M., *et al.* Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med*, 2012. 157: 681.
<https://www.ncbi.nlm.nih.gov/pubmed/23165659>
182. Eardley, I., *et al.* Factors associated with preference for sildenafil citrate and tadalafil for treating erectile dysfunction in men naive to phosphodiesterase 5 inhibitor therapy: post hoc analysis of data from a multicentre, randomized, open-label, crossover study. *BJU Int*, 2007. 100: 122.
<https://www.ncbi.nlm.nih.gov/pubmed/17552960>
183. Cui, H., *et al.* Efficacy and safety of long-term tadalafil 5 mg once daily combined with sildenafil 50 mg as needed at the early stage of treatment for patients with erectile dysfunction. *Andrologia*, 2014. 47: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/24387078>
184. Park, M.G., *et al.* The efficacy of combination treatment with injectable testosterone undecanoate and daily tadalafil for erectile dysfunction with testosterone deficiency syndrome. *J Sex Med*, 2015. 12: 966
<https://www.ncbi.nlm.nih.gov/pubmed/25648342>
185. Levine, L.A., *et al.* Vacuum constriction and external erection devices in erectile dysfunction. *Urol Clin North Am*, 2001. 28: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/11402585>
186. Yuan, J., *et al.* Vacuum therapy in erectile dysfunction--science and clinical evidence. *Int J Impot Res*, 2010. 22: 211.
<https://www.ncbi.nlm.nih.gov/pubmed/20410903>
187. Cookson, M.S., *et al.* Long-term results with vacuum constriction device. *J Urol*, 1993. 149: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/8426404>
188. Gruenwald, I., *et al.* Shockwave treatment of erectile dysfunction. *Ther Adv Urol*, 2013. 5: 95.
<https://www.ncbi.nlm.nih.gov/pubmed/23554844>

189. Gruenwald, I., *et al.* Low-intensity extracorporeal shock wave therapy--a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. *J Sex Med*, 2012. 9: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/22008059>
190. Chung, E., *et al.* Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial. *BJU Int*, 2015. 5: 46.
<https://www.ncbi.nlm.nih.gov/pubmed/25828173>
191. Olsen, A.B., *et al.* Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. *Scand J Urol*, 2015. 49: 329.
<https://www.ncbi.nlm.nih.gov/pubmed/25470423>
192. Vardi, Y., *et al.* Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. *Eur Urol*, 2010. 58: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/20451317>
193. Lu, Z., *et al.* Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. *Eur Urol*, 2017. 71: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/27321373>
194. Coombs, P.G., *et al.* A review of outcomes of an intracavernosal injection therapy programme. *BJU Int*, 2012. 110: 1787.
<https://www.ncbi.nlm.nih.gov/pubmed/22564343>
195. Shabsigh, R., *et al.* Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional actis: a comparative, randomized, crossover, multicenter study. *Urology*, 2000. 55: 109.
<https://www.ncbi.nlm.nih.gov/pubmed/10654905>
196. Eardley, I., *et al.* Pharmacotherapy for erectile dysfunction. *J Sex Med*, 2010. 7: 524.
<https://www.ncbi.nlm.nih.gov/pubmed/20092451>
197. Lakin, M.M., *et al.* Intracavernous injection therapy: analysis of results and complications. *J Urol*, 1990. 143: 1138.
<https://www.ncbi.nlm.nih.gov/pubmed/2342174>
198. Moriel, E.Z., *et al.* Sodium bicarbonate alleviates penile pain induced by intracavernous injections for erectile dysfunction. *J Urol*, 1993. 149: 1299.
<https://www.ncbi.nlm.nih.gov/pubmed/8386779>
199. Gupta, R., *et al.* Predictors of success and risk factors for attrition in the use of intracavernous injection. *J Urol*, 1997. 157: 1681.
<https://www.ncbi.nlm.nih.gov/pubmed/9112505>
200. Sundaram, C.P., *et al.* Long-term follow-up of patients receiving injection therapy for erectile dysfunction. *Urology*, 1997. 49: 932.
<https://www.ncbi.nlm.nih.gov/pubmed/9187703>
201. Vardi, Y., *et al.* Logistic regression and survival analysis of 450 impotent patients treated with injection therapy: long-term dropout parameters. *J Urol*, 2000. 163: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/10647656>
202. Buvat, J., *et al.* Double-blind multicenter study comparing alprostadil alpha-cyclodextrin with moxislyte chlorhydrate in patients with chronic erectile dysfunction. *J Urol*, 1998. 159: 116.
<https://www.ncbi.nlm.nih.gov/pubmed/9400450>
203. Mulhall, J.P., *et al.* Intracavernosal forskolin: role in management of vasculogenic impotence resistant to standard 3-agent pharmacotherapy. *J Urol*, 1997. 158: 1752.
<https://www.ncbi.nlm.nih.gov/pubmed/9334594>
204. Bechara, A., *et al.* Comparative study of papaverine plus phentolamine versus prostaglandin E1 in erectile dysfunction. *J Urol*, 1997. 157: 2132.
<https://www.ncbi.nlm.nih.gov/pubmed/9146599>
205. McMahon CG, *et al.* A comparison of the response to the intracavernosal injection of papaverine and phentolamine, prostaglandin E1 and a combination of all three agents in the management of impotence *J Urol*, 1999. 162. [No abstract available].
206. Dinsmore, W.W., *et al.* Vasoactive intestinal polypeptide/phentolamine for intracavernosal injection in erectile dysfunction. *BJU Int*, 2008. 102: 933.
<https://www.ncbi.nlm.nih.gov/pubmed/18485029>
207. McMahon, C.G., *et al.* Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple agent intracorporeal injection therapy. *J Urol*, 1999. 162: 1992.
<https://www.ncbi.nlm.nih.gov/pubmed/10569554>

208. Padma-Nathan, H., *et al.* Treatment of men with erectile dysfunction with transurethral alprostadil. Medicated Urethral System for Erection (MUSE) Study Group. *N Engl J Med*, 1997. 336: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/8970933>
209. Costa, P., *et al.* Intraurethral alprostadil for erectile dysfunction: a review of the literature. *Drugs*, 2012. 72: 2243.
<https://www.ncbi.nlm.nih.gov/pubmed/23170913>
210. Mulhall, J.P., *et al.* Analysis of the consistency of intraurethral prostaglandin E(1) (MUSE) during at-home use. *Urology*, 2001. 58: 262.
<https://www.ncbi.nlm.nih.gov/pubmed/11489714>
211. Yeager, J., *et al.* Retention and migration of alprostadil cream applied topically to the glans meatus for erectile dysfunction. *Int J Impot Res*, 2005. 17: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/15538395>
212. Padma-Nathan, H., *et al.* An integrated analysis of alprostadil topical cream for the treatment of erectile dysfunction in 1732 patients. *Urology*, 2006. 68: 386.
<https://www.ncbi.nlm.nih.gov/pubmed/16904458>
213. Antonini, G., *et al.* Minimally invasive infrapubic inflatable penile prosthesis implant for erectile dysfunction: Evaluation of efficacy, satisfaction profile and complications. *Int J Impot Res*, 2016. 28: 4.
<https://www.ncbi.nlm.nih.gov/pubmed/26657316>
214. Martinez-Salamanca, J.I., *et al.* Penile prosthesis surgery in patients with corporal fibrosis: a state of the art review. *J Sex Med*, 2011. 8: 1880.
<https://www.ncbi.nlm.nih.gov/pubmed/21492405>
215. Montague, D.K. Penile prosthesis implantation in the era of medical treatment for erectile dysfunction. *Urol Clin North Am*, 2011. 38: 217.
<https://www.ncbi.nlm.nih.gov/pubmed/21621088>
216. Montague, D.K., *et al.* Penile prosthesis implantation. *Urol Clin North Am*, 2001. 28: 355.
<https://www.ncbi.nlm.nih.gov/pubmed/11402587>
217. Mulcahy, J.J., *et al.* The penile implant for erectile dysfunction. *J Sex Med*, 2004. 1: 98.
<https://www.ncbi.nlm.nih.gov/pubmed/16422990>
218. Bettocchi, C., *et al.* Patient and partner satisfaction after AMS inflatable penile prosthesis implant. *J Sex Med*, 2010. 7: 304.
<https://www.ncbi.nlm.nih.gov/pubmed/19758282>
219. Chung, E., *et al.* Penile prosthesis implantation for the treatment for male erectile dysfunction: clinical outcomes and lessons learnt after 955 procedures. *World J Urol*, 2013. 31: 591.
<https://www.ncbi.nlm.nih.gov/pubmed/22457032>
220. Falcone, M., *et al.* Prospective analysis of the surgical outcomes and patients' satisfaction rate after the AMS Spectra penile prosthesis implantation. *Urology*, 2013. 82: 373.
<https://www.ncbi.nlm.nih.gov/pubmed/23791218>
221. Henry, G.D., *et al.* A survey of patients with inflatable penile prostheses: assessment of timing and frequency of intercourse and analysis of implant durability. *J Sex Med*, 2012. 9: 1715.
<https://www.ncbi.nlm.nih.gov/pubmed/22568579>
222. Kim, D.S., *et al.* AMS 700CX/CXM inflatable penile prosthesis has high mechanical reliability at long-term follow-up. *J Sex Med*, 2010. 7: 2602.
<https://www.ncbi.nlm.nih.gov/pubmed/20384938>
223. Lux, M., *et al.* Outcomes and satisfaction rates for the redesigned 2-piece penile prosthesis. *J Urol*, 2007. 177: 262.
<https://www.ncbi.nlm.nih.gov/pubmed/17162061>
224. Natali, A., *et al.* Penile implantation in Europe: successes and complications with 253 implants in Italy and Germany. *J Sex Med*, 2008. 5: 1503.
<https://www.ncbi.nlm.nih.gov/pubmed/18410306>
225. Lee, D., *et al.* Simultaneous penile prosthesis and male sling/artificial urinary sphincter. *Asian J Androl*, 2013. 15: 10.
<https://www.ncbi.nlm.nih.gov/pubmed/23202702>
226. Lee, D., *et al.* Combination surgery for erectile dysfunction and male incontinence. *Curr Urol Rep*, 2011. 12: 461.
<https://www.ncbi.nlm.nih.gov/pubmed/21956147>
227. Segal, R.L., *et al.* Combined inflatable penile prosthesis-artificial urinary sphincter implantation: no increased risk of adverse events compared to single or staged device implantation. *J Urol*, 2013. 190: 2183.
<https://www.ncbi.nlm.nih.gov/pubmed/23831315>
228. Pisano, F., *et al.* The importance of psychosexual counselling in the re-establishment of organic and

- erotic functions after penile prosthesis implantation. *Int J Impot Res*, 2015. 27: 197.
<https://www.ncbi.nlm.nih.gov/pubmed/26268774>
229. Carson, C.C., *et al.* Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. AMS 700CX Study Group. *J Urol*, 2000. 164: 376.
<https://www.ncbi.nlm.nih.gov/pubmed/10893589>
230. Wilson, S.K., *et al.* Comparison of mechanical reliability of original and enhanced Mentor Alpha I penile prosthesis. *J Urol*, 1999. 162: 715.
<https://www.ncbi.nlm.nih.gov/pubmed/10458350>
231. Mandava, S.H., *et al.* Infection retardant coated inflatable penile prostheses decrease the incidence of infection: a systematic review and meta-analysis. *J Urol*, 2012. 188: 1855.
<https://www.ncbi.nlm.nih.gov/pubmed/22999690>
232. Mulcahy, J.J. Long-term experience with salvage of infected penile implants. *J Urol*, 2000. 163: 481.
<https://www.ncbi.nlm.nih.gov/pubmed/10647660>
233. Trost, L.W., *et al.* Long-term outcomes of penile prostheses for the treatment of erectile dysfunction. *Expert Rev Med Devices*, 2013. 10: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/23668707>
234. Carson, C.C., 3rd, *et al.* Long-term infection outcomes after original antibiotic impregnated inflatable penile prosthesis implants: up to 7.7 years of followup. *J Urol*, 2011. 185: 614.
<https://www.ncbi.nlm.nih.gov/pubmed/21168870>
235. Darouiche, R.O., *et al.* North American consensus document on infection of penile prostheses. *Urology*, 2013. 82: 937.
<https://www.ncbi.nlm.nih.gov/pubmed/23958508>
236. Serefoglu, E.C., *et al.* Long-term revision rate due to infection in hydrophilic-coated inflatable penile prostheses: 11-year follow-up. *J Sex Med*, 2012. 9: 2182.
<https://www.ncbi.nlm.nih.gov/pubmed/22759917>
237. Zargaroff, S., *et al.* National trends in the treatment of penile prosthesis infections by explantation alone vs. immediate salvage and reimplantation. *J Sex Med*, 2014. 11: 1078.
<https://www.ncbi.nlm.nih.gov/pubmed/24628707>
238. Henry, G.D., *et al.* An outcomes analysis of over 200 revision surgeries for penile prosthesis implantation: a multicenter study. *J Sex Med*, 2012. 9: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/22082149>
239. Levine, L.A., *et al.* Standard operating procedures for Peyronie's disease. *J Sex Med*, 2013. 10: 230.
<https://www.ncbi.nlm.nih.gov/pubmed/23211057>
240. Pineda, M., *et al.* Penile Prosthesis Infections-A Review of Risk Factors, Prevention, and Treatment. *Sex Med Rev*, 2016. 4: 389.
<https://www.ncbi.nlm.nih.gov/pubmed/27872031>
241. Habous, M., *et al.* Conservative Therapy is an Effective Option in Patients With Localized Infection After Penile Implant Surgery. *J Sex Med*, 2016. 13: 972.
<https://www.ncbi.nlm.nih.gov/pubmed/27162191>
242. Levine, L.A., *et al.* Penile Prosthesis Surgery: Current Recommendations From the International Consultation on Sexual Medicine. *J Sex Med*, 2016. 13: 489.
<https://www.ncbi.nlm.nih.gov/pubmed/27045255>
243. Waldinger, M.D. The neurobiological approach to premature ejaculation. *J Urol*, 2002. 168: 2359.
<https://www.ncbi.nlm.nih.gov/pubmed/12441918>
244. Laumann, E.O., *et al.* Sexual dysfunction in the United States: prevalence and predictors. *JAMA*, 1999. 281: 537.
<https://www.ncbi.nlm.nih.gov/pubmed/10022110>
245. Porst, H., *et al.* The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. *Eur Urol*, 2007. 51: 816.
<https://www.ncbi.nlm.nih.gov/pubmed/16934919>
246. Waldinger, M.D., *et al.* The use of old and recent DSM definitions of premature ejaculation in observational studies: a contribution to the present debate for a new classification of PE in the DSM-V. *J Sex Med*, 2008. 5: 1079.
<https://www.ncbi.nlm.nih.gov/pubmed/18331260>
247. Serefoglu, E.C., *et al.* Prevalence of the complaint of ejaculating prematurely and the four premature ejaculation syndromes: results from the Turkish Society of Andrology Sexual Health Survey. *J Sex Med*, 2011. 8: 540.
<https://www.ncbi.nlm.nih.gov/pubmed/21054799>
248. Althof, S.E., *et al.* An update of the International Society of Sexual Medicine's guidelines for the

- diagnosis and treatment of premature ejaculation (PE). *J Sex Med*, 2014. 11: 1392.
<https://www.ncbi.nlm.nih.gov/pubmed/24848686>
249. McMahon, C.G., *et al.* Disorders of orgasm and ejaculation in men. *J Sex Med*, 2004. 1: 58.
<https://www.ncbi.nlm.nih.gov/pubmed/16422984>
250. Laumann, E.O., *et al.* Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res*, 2005. 17: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/15215881>
251. Corona, G., *et al.* Interplay Between Premature Ejaculation and Erectile Dysfunction: A Systematic Review and Meta-Analysis. *J Sex Med*, 2015. 12 :2291.
<https://www.ncbi.nlm.nih.gov/pubmed/26552599>
252. Carson, C., *et al.* Premature ejaculation: definition and prevalence. *Int J Impot Res*, 2006. 18 Suppl 1: S5.
<https://www.ncbi.nlm.nih.gov/pubmed/16953247>
253. Richardson, D., *et al.* Premature ejaculation--does country of origin tell us anything about etiology? *J Sex Med*, 2005. 2: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/16422845>
254. Waldinger, M.D., *et al.* Familial occurrence of primary premature ejaculation. *Psychiatr Genet*, 1998. 8: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/9564687>
255. Screponi, E., *et al.* Prevalence of chronic prostatitis in men with premature ejaculation. *Urology*, 2001. 58: 198.
<https://www.ncbi.nlm.nih.gov/pubmed/11489699>
256. Shamloul, R., *et al.* Chronic prostatitis in premature ejaculation: a cohort study in 153 men. *J Sex Med*, 2006. 3: 150.
<https://www.ncbi.nlm.nih.gov/pubmed/16409229>
257. Lee, J.H., *et al.* Relationship between premature ejaculation and chronic prostatitis/chronic pelvic pain syndrome. *J Sex Med*, 2015. 12: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/25475760>
258. Carani, C., *et al.* Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. *J Clin Endocrinol Metab*, 2005. 90: 6472.
<https://www.ncbi.nlm.nih.gov/pubmed/16204360>
259. Majzoub, A., *et al.* Premature ejaculation in type II diabetes mellitus patients: Association with glycemic control. *Transl Androl Urol*, 2016. 5: 248.
<https://www.ncbi.nlm.nih.gov/pubmed/27141454>
260. Dunn, K.M., *et al.* Association of sexual problems with social, psychological, and physical problems in men and women: a cross sectional population survey. *J Epidemiol Community Health*, 1999. 53: 144.
<https://www.ncbi.nlm.nih.gov/pubmed/10396490>
261. El-Nashaar, A., *et al.* Antibiotic treatment can delay ejaculation in patients with premature ejaculation and chronic bacterial prostatitis. *J Sex Med*, 2007. 4: 491.
<https://www.ncbi.nlm.nih.gov/pubmed/17367444>
262. Palmieri, A., *et al.* Ejaculatory abstinence influences intravaginal ejaculatory latency time: results from a prospective randomized trial. *Urol Int*, 2012. 88: 459.
<https://www.ncbi.nlm.nih.gov/pubmed/22456105>
263. Rowland, D., *et al.* Self-reported premature ejaculation and aspects of sexual functioning and satisfaction. *J Sex Med*, 2004. 1: 225.
<https://www.ncbi.nlm.nih.gov/pubmed/16429622>
264. Rowland, D.L., *et al.* The psychological burden of premature ejaculation. *J Urol*, 2007. 177: 1065.
<https://www.ncbi.nlm.nih.gov/pubmed/16429622>
265. Symonds, T., *et al.* How does premature ejaculation impact a man s life? *J Sex Marital Ther*, 2003. 29: 361.
<https://www.ncbi.nlm.nih.gov/pubmed/14504007>
266. Riley, A., *et al.* Treatment of premature ejaculation. *Int J Clin Pract*, 2006. 60: 694.
<https://www.ncbi.nlm.nih.gov/pubmed/16805755>
267. Byers, E.S., *et al.* Premature or rapid ejaculation: heterosexual couples' perceptions of men's ejaculatory behavior. *Arch Sex Behav*, 2003. 32: 261.
<https://www.ncbi.nlm.nih.gov/pubmed/12807298>

268. Solursh, D.S., *et al.* The human sexuality education of physicians in North American medical schools. *Int J Impot Res*, 2003. 15 Suppl 5: S41.
<https://www.ncbi.nlm.nih.gov/pubmed/14551576>
269. Sotomayor, M. The burden of premature ejaculation: the patient's perspective. *J Sex Med*, 2005. 2 Suppl 2: 110.
<https://www.ncbi.nlm.nih.gov/pubmed/16422797>
270. American Psychiatric Association., *Diagnostic and Statistical Manual of Mental Disorders*. 4th edn. Text Revision. [Access date February 2014]
Revision. 2000, American Psychiatric Publishing Inc: Washington, DC.
<http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596>
271. DSM, V., American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. 2013, Arlington, VA [access date: 1 June 2013]. [dsm.psychiatryonline.org](http://www.dsm5.org/psychiatrists/practice/dsm).
<http://www.dsm5.org/psychiatrists/practice/dsm>
272. Serefoglu, E.C., *et al.* An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. *J Sex Med*, 2014. 11: 1423.
<https://www.ncbi.nlm.nih.gov/pubmed/24848805>
273. Waldinger, M.D., *et al.* Changing paradigms from a historical DSM-III and DSM-IV view toward an evidence-based definition of premature ejaculation. Part II--proposals for DSM-V and ICD-11. *J Sex Med*, 2006. 3: 693.
<https://www.ncbi.nlm.nih.gov/pubmed/24848805>
274. Waldinger, M.D. Premature ejaculation: state of the art. *Urol Clin North Am*, 2007. 34: 591.
<https://www.ncbi.nlm.nih.gov/pubmed/17352514>
275. Shabsigh, R. Diagnosing premature ejaculation: a review. *J Sex Med*, 2006. 3 Suppl 4: 318.
<https://www.ncbi.nlm.nih.gov/pubmed/16939476>
276. Sharlip, I. Diagnosis and treatment of premature ejaculation: the physician's perspective. *J Sex Med*, 2005. 2 Suppl 2: 103.
<https://www.ncbi.nlm.nih.gov/pubmed/16422796>
277. Rowland, D.L., *et al.* Premature ejaculation: psychophysiological considerations in theory, research, and treatment. *Annu Rev Sex Res*, 1997. 8: 224.
<https://www.ncbi.nlm.nih.gov/pubmed/10051895>
278. Althof, S.E. Prevalence, characteristics and implications of premature ejaculation/rapid ejaculation. *J Urol*, 2006. 175: 842.
<https://www.ncbi.nlm.nih.gov/pubmed/16469562>
279. Althof, S.E., *et al.* Patient reported outcomes used in the assessment of premature ejaculation. *Urol Clin North Am*, 2007. 34: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/17983898>
280. Giuliano, F., *et al.* Premature ejaculation: results from a five-country European observational study. *Eur Urol*, 2008. 53: 1048.
<https://www.ncbi.nlm.nih.gov/pubmed/17950985>
281. Patrick, D.L., *et al.* Premature ejaculation: an observational study of men and their partners. *J Sex Med*, 2005. 2: 358.
<https://www.ncbi.nlm.nih.gov/pubmed/16422867>
282. Patrick, D.L., *et al.* Interrelationships among measures of premature ejaculation: the central role of perceived control. *J Sex Med*, 2007. 4: 780.
<https://www.ncbi.nlm.nih.gov/pubmed/17419817>
283. Althof, S.E., *et al.* International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. *J Sex Med*, 2010. 7: 2947.
<https://www.ncbi.nlm.nih.gov/pubmed/21050394>
284. Rosen, R.C., *et al.* Correlates to the clinical diagnosis of premature ejaculation: results from a large observational study of men and their partners. *J Urol*, 2007. 177: 1059.
<https://www.ncbi.nlm.nih.gov/pubmed/17296411>
285. Lee, W.K., *et al.* Can estimated intravaginal ejaculatory latency time be used interchangeably with stopwatch-measured intravaginal ejaculatory latency time for the diagnosis of lifelong premature ejaculation? *Urology*, 2015. 85: 375.
<https://www.ncbi.nlm.nih.gov/pubmed/25623693>
286. Kempeneers, P., *et al.* Functional and psychological characteristics of belgian men with premature ejaculation and their partners. *Arch Sex Behav*, 2013. 42: 51.
<https://www.ncbi.nlm.nih.gov/pubmed/22695640>

287. Symonds, T., *et al.* Further evidence of the reliability and validity of the premature ejaculation diagnostic tool. *Int J Impot Res*, 2007. 19: 521.
<https://www.ncbi.nlm.nih.gov/pubmed/17568761>
288. Symonds, T., *et al.* Development and validation of a premature ejaculation diagnostic tool. *Eur Urol*, 2007. 52: 565.
<https://www.ncbi.nlm.nih.gov/pubmed/16681472>
289. Arafa, M., *et al.* Development and evaluation of the Arabic Index of Premature Ejaculation (AIPE). *J Sex Med*, 2007. 4: 1750.
<https://www.ncbi.nlm.nih.gov/pubmed/17970977>
290. McMahon, C.G., *et al.* Premature ejaculation and erectile dysfunction prevalence and attitudes in the Asia-Pacific region. *J Sex Med*, 2012. 9: 454.
<https://www.ncbi.nlm.nih.gov/pubmed/22023395>
291. McMahon, C.G. Ejaculatory latency vs. patient-reported outcomes (PROs) as study end points in premature ejaculation clinical trials. *Eur Urol*, 2007. 52: 321.
<https://www.ncbi.nlm.nih.gov/pubmed/17445975>
292. Althof, S., *et al.* Development and validation of a new questionnaire to assess sexual satisfaction, control, and distress associated with premature ejaculation. *J Sex Med*, 2006. 3: 465.
<https://www.ncbi.nlm.nih.gov/pubmed/16681472>
293. Rosen, R.C., *et al.* Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. *Urology*, 2007. 69: 805.
<https://www.ncbi.nlm.nih.gov/pubmed/17482908>
294. Semans, J.H. Premature ejaculation: a new approach. *South Med J*, 1956. 49: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/13311629>
295. Masters, H.M., *et al.*, Human Sexual Inadequacy. 1970. [No abstract available].
296. de Carufel, F., *et al.* Effects of a new functional-sexological treatment for premature ejaculation. *J Sex Marital Ther*, 2006. 32: 97.
<https://www.ncbi.nlm.nih.gov/pubmed/16418103>
297. Grenier, G., *et al.* Rapid ejaculation: a review of conceptual, etiological, and treatment issues. *Arch Sex Behav*, 1995. 24: 447.
<https://www.ncbi.nlm.nih.gov/pubmed/7661658>
298. Metz, M.E., *et al.* Premature ejaculation: a psychophysiological review. *J Sex Marital Ther*, 1997. 23: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/9094032>
299. Cooper, K., *et al.* Behavioral Therapies for Management of Premature Ejaculation: A Systematic Review. *Sex Med*, 2015. 3: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/26468381>
300. Abdel-Hamid, I.A., *et al.* Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. *Int J Impot Res*, 2001. 13: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/11313839>
301. De Amicis, L.A., *et al.* Clinical follow-up of couples treated for sexual dysfunction. *Arch Sex Behav*, 1985. 14: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/4084048>
302. Hawton, K., *et al.* Long-term outcome of sex therapy. *Behav Res Ther*, 1986. 24: 665.
<https://www.ncbi.nlm.nih.gov/pubmed/3800838>
303. Cormio, L., *et al.* The Combination of Dapoxetine and Behavioral Treatment Provides Better Results than Dapoxetine Alone in the Management of Patients with Lifelong Premature Ejaculation. *J Sex Med*, 2015. 12: 1609.
<https://www.ncbi.nlm.nih.gov/pubmed/26077706>
304. Modi, N.B., *et al.* Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *J Clin Pharmacol*, 2006. 46: 301.
<https://www.ncbi.nlm.nih.gov/pubmed/16490806>
305. McMahon, C.G. Dapoxetine: a new option in the medical management of premature ejaculation. *Ther Adv Urol*, 2012. 4: 233.
<https://www.ncbi.nlm.nih.gov/pubmed/23024705>
306. McMahon, C.G., *et al.* Oral agents for the treatment of premature ejaculation: review of efficacy and safety in the context of the recent International Society for Sexual Medicine criteria for lifelong premature ejaculation. *J Sex Med*, 2011. 8: 2707.
<https://www.ncbi.nlm.nih.gov/pubmed/21771283>

307. Porst, H., *et al.* Baseline characteristics and treatment outcomes for men with acquired or lifelong premature ejaculation with mild or no erectile dysfunction: integrated analyses of two phase 3 dapoxetine trials. *J Sex Med*, 2010. 7: 2231.
<https://www.ncbi.nlm.nih.gov/pubmed/20412423>
308. McMahon, C., *et al.* The Asia-Pacific Flexible Dose Study of Dapoxetine and Patient Satisfaction in Premature Ejaculation Therapy: The PASSION Study. *Sex Med*, 2016. 4: e18.
<https://www.ncbi.nlm.nih.gov/pubmed/26944775>
309. Yue, F.G., *et al.* Efficacy of Dapoxetine for the Treatment of Premature Ejaculation: A Meta-analysis of Randomized Clinical Trials on Intravaginal Ejaculatory Latency Time, Patient-reported Outcomes, and Adverse Events. *Urology*, 2015. 85: 856.
<https://www.ncbi.nlm.nih.gov/pubmed/25817107>
310. McMahon, C.G., *et al.* Efficacy and safety of dapoxetine for the treatment of premature ejaculation: integrated analysis of results from five phase 3 trials. *J Sex Med*, 2011. 8: 524.
<https://www.ncbi.nlm.nih.gov/pubmed/21059176>
311. Verze, P., *et al.* Comparison of Treatment of Emergent Adverse Events in Men With Premature Ejaculation Treated With Dapoxetine and Alternate Oral Treatments: Results From a Large Multinational Observational Trial. *J Sex Med*, 2016. 13: 194.
<https://www.ncbi.nlm.nih.gov/pubmed/26805941>
312. McMahon, C.G., *et al.* Efficacy and safety of dapoxetine in men with premature ejaculation and concomitant erectile dysfunction treated with a phosphodiesterase type 5 inhibitor: randomized, placebo-controlled, phase III study. *J Sex Med*, 2013. 10: 2312.
<https://www.ncbi.nlm.nih.gov/pubmed/23845016>
313. Miron, V., *et al.* Results from a prospective observational study of men with premature ejaculation treated with dapoxetine or alternative care: the PAUSE study. *Eur Urol*, 2014. 65: 733.
<https://www.ncbi.nlm.nih.gov/pubmed/23993257>
314. Giuliano, F. 5-Hydroxytryptamine in premature ejaculation: opportunities for therapeutic intervention. *Trends Neurosci*, 2007. 30: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/17169440>
315. Borgdorff, A.J., *et al.* Ejaculation elicited by microstimulation of lumbar spinothalamic neurons. *Eur Urol*, 2008. 54: 449.
<https://www.ncbi.nlm.nih.gov/pubmed/18394782>
316. Truitt, W.A., *et al.* Identification of a potential ejaculation generator in the spinal cord. *Science*, 2002. 297: 1566.
<https://www.ncbi.nlm.nih.gov/pubmed/12202834>
317. Olivier, B., *et al.* Serotonin, serotonergic receptors, selective serotonin reuptake inhibitors and sexual behaviour. *Int Clin Psychopharmacol*, 1998. 13 Suppl 6: S9.
<https://www.ncbi.nlm.nih.gov/pubmed/9728669>
318. Waldinger, M.D. Premature ejaculation: definition and drug treatment. *Drugs*, 2007. 67: 547.
<https://www.ncbi.nlm.nih.gov/pubmed/17352514>
319. Waldinger, M.D., *et al.* Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry*, 1994. 151: 1377.
<https://www.ncbi.nlm.nih.gov/pubmed/8067497>
320. Waldinger, M.D., *et al.* Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res*, 2004. 16: 369.
<https://www.ncbi.nlm.nih.gov/pubmed/14961051>
321. Castiglione, F., *et al.* Current Pharmacological Management of Premature Ejaculation: A Systematic Review and Meta-analysis. *Eur Urol*, 2016. 69: 904.
<https://www.ncbi.nlm.nih.gov/pubmed/26749092>
322. Waldinger, M.D., *et al.* Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol*, 1998. 18: 274.
<https://www.ncbi.nlm.nih.gov/pubmed/9690692>
323. Waldinger, M.D., *et al.* SSRIs and ejaculation: a double-blind, randomized, fixed-dose study with paroxetine and citalopram. *J Clin Psychopharmacol*, 2001. 21: 556.
<https://www.ncbi.nlm.nih.gov/pubmed/11763001>
324. Waldinger, M.D., *et al.* On-demand treatment of premature ejaculation with clomipramine and paroxetine: a randomized, double-blind fixed-dose study with stopwatch assessment. *Eur Urol*, 2004. 46: 510.
<https://www.ncbi.nlm.nih.gov/pubmed/15363569>

325. Kim, S.W., *et al.* Short-term analysis of the effects of as needed use of sertraline at 5 PM for the treatment of premature ejaculation. *Urology*, 1999. 54: 544.
<https://www.ncbi.nlm.nih.gov/pubmed/10475369>
326. McMahon, C.G., *et al.* Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. *J Urol*, 1999. 161: 1826.
<https://www.ncbi.nlm.nih.gov/pubmed/10332446>
327. Morales, A., *et al.* A review of the current status of topical treatments for premature ejaculation. *BJU Int*, 2007. 100: 493.
<https://www.ncbi.nlm.nih.gov/pubmed/17608824>
328. Sachs, B.D., *et al.* Maintenance of erection of penile glans, but not penile body, after transection of rat cavernous nerves. *J Urol*, 1991. 146: 900.
<https://www.ncbi.nlm.nih.gov/pubmed/1875517>
329. Wieder, J.A., *et al.* Anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation in men with spinal cord injuries. *Urology*, 2000. 55: 915.
<https://www.ncbi.nlm.nih.gov/pubmed/10840108>
330. Martyn- St. James, M., *et al.* Topical anaesthetics for premature ejaculation: A systematic review and meta-analysis. *Sex Health*, 2016. 13: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/26599522>
331. Atikeler, M.K., *et al.* Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia*, 2002. 34: 356.
<https://www.ncbi.nlm.nih.gov/pubmed/12472618>
332. Busato, W., *et al.* Topical anaesthetic use for treating premature ejaculation: a double-blind, randomized, placebo-controlled study. *BJU Int*, 2004. 93: 1018.
<https://www.ncbi.nlm.nih.gov/pubmed/15142155>
333. Wyllie, M.G., *et al.* The role of local anaesthetics in premature ejaculation. *BJU Int*, 2012. 110: E943.
<https://www.ncbi.nlm.nih.gov/pubmed/22758648>
334. Frink, M.C., *et al.* Influence of tramadol on neurotransmitter systems of the rat brain. *Arzneimittelforschung*, 1996. 46: 1029.
<https://www.ncbi.nlm.nih.gov/pubmed/8955860>
335. FDA, U. Warning letter to William Weldon, CEO & Chairman of Johnson & Johnson, regarding Ultram-ER web advertisement. 2009.
<http://www.fda.gov/downloads/Drugs/.../UCM153130.pdf>
336. Bar-Or, D., *et al.* A randomized double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of the tramadol orally disintegrating tablet for the treatment of premature ejaculation within less than 2 minutes. *Eur Urol*, 2012. 61: 736.
<https://www.ncbi.nlm.nih.gov/pubmed/21889833>
337. Kurkar, A., *et al.* A randomized, double-blind, placebo-controlled, crossover trial of “on-demand” tramadol for treatment of premature ejaculation. *Urol Ann*, 2015. 7: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/25835132>
338. Martyn-St James, M., *et al.* Tramadol for premature ejaculation: a systematic review and meta-analysis. [Review]. *BMC Urol*, 2015. 15: 6.
<https://www.ncbi.nlm.nih.gov/pubmed/25636495>
339. Kirby, E.W., *et al.* Tramadol for the management of premature ejaculation: A timely systematic review. *Int J Impot Res*, 2015. 27: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/25971856>
340. McMahon, C.G., *et al.* Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *J Sex Med*, 2005. 2: 368.
<https://www.ncbi.nlm.nih.gov/pubmed/16422868>
341. Salonia, A., *et al.* A prospective study comparing paroxetine alone versus paroxetine plus sildenafil in patients with premature ejaculation. *J Urol*, 2002. 168: 2486.
<https://www.ncbi.nlm.nih.gov/pubmed/12441946>
342. Zhang, X.S., *et al.* [Comparison between sildenafil plus sertraline and sertraline alone in the treatment of premature ejaculation]. *Zhonghua Nan Ke Xue*, 2005. 11: 520.
<https://www.ncbi.nlm.nih.gov/pubmed/16078671>
343. Chen, J., *et al.* Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating premature ejaculation. *Urology*, 2003. 61: 197.
<https://www.ncbi.nlm.nih.gov/pubmed/12559295>
344. Polat, E.C., *et al.* Combination therapy with selective serotonin reuptake inhibitors and phosphodiesterase-5 inhibitors in the treatment of premature ejaculation. *Andrologia*, 2015. 47: 487.
<https://www.ncbi.nlm.nih.gov/pubmed/24811578>

345. Tang, W., *et al.* [Clinical efficacy of Viagra with behavior therapy against premature ejaculation]. *Zhonghua Nan Ke Xue*, 2004. 10: 366.
<https://www.ncbi.nlm.nih.gov/pubmed/15190831>
346. McMahon, C.G., *et al.* Efficacy of type-5 phosphodiesterase inhibitors in the drug treatment of premature ejaculation: a systematic review. *BJU Int*, 2006. 98: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/16879663>
347. Wang, W.F., *et al.* Phosphodiesterase 5 inhibitors in the treatment of premature ejaculation. *Int J Androl*, 2006. 29: 503.
<https://www.ncbi.nlm.nih.gov/pubmed/16573707>
348. Bai, Y., *et al.* Selective Serotonin Reuptake Inhibitors Plus Phosphodiesterase-5 Inhibitors for Premature Ejaculation: A Systematic Review and Meta-analysis. *Urology*, 2015. 86: 758.
<https://www.ncbi.nlm.nih.gov/pubmed/26247816>
349. Moudi, E., *et al.* Comparison Between Tadalafil Plus Paroxetine and Paroxetine Alone in the Treatment of Premature Ejaculation. *Nephrourol Mon*, 2016. 8: e32286.
<https://www.ncbi.nlm.nih.gov/pubmed/26981497>
350. Sun, Y., *et al.* Efficacy of Phosphodiesterase-5 Inhibitor in Men With Premature Ejaculation: A New Systematic Review and Meta-analysis. [Review]. *Urology*, 2015. 86: 947.
<https://www.ncbi.nlm.nih.gov/pubmed/26278825>
351. Lue, T.F., *et al.* Summary of the recommendations on sexual dysfunctions in men. *J Sex Med*, 2004. 1: 6.
<https://www.ncbi.nlm.nih.gov/pubmed/16422979>
352. Yachia, D., *et al.* The incidence of congenital penile curvature. *J Urol*, 1993. 150: 1478.
<https://www.ncbi.nlm.nih.gov/pubmed/8411431>
353. Montag, S., *et al.* Abnormalities of penile curvature: chordee and penile torsion. *Sci World J*, 2011. 11: 1470.
<https://www.ncbi.nlm.nih.gov/pubmed/21805016>
354. Baskin, L.S., *et al.* Penile curvature. *Urology*, 1996. 48: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/8804484>
355. Menon, V., *et al.* Do adult men with untreated ventral penile curvature have adverse outcomes? *J Pediatr Urol*, 2016. 12: 31.e1.
<https://www.ncbi.nlm.nih.gov/pubmed/26776946>
356. Shaeer, O. Shaeer's corporal rotation for length-preserving correction of penile curvature: modifications and 3-year experience. *J Sex Med*, 2008. 5: 2716.
<https://www.ncbi.nlm.nih.gov/pubmed/18624969>
357. Shaeer, O., *et al.* Shaeer's Corporal Rotation III: Shortening-Free Correction of Congenital Penile Curvature-The Noncorporotomy Technique. *Eur Urol*, 2016. 69: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/26298209>
358. Bar Yosef, Y., *et al.* Midline dorsal plication technique for penile curvature repair. *J Urol*, 2004. 172: 1368.
<https://www.ncbi.nlm.nih.gov/pubmed/15371846>
359. Ebbelohj, J., *et al.* Congenital penile angulation. *Br J Urol*, 1987. 60: 264.
<https://www.ncbi.nlm.nih.gov/pubmed/3676675>
360. Hayashi, Y., *et al.* Modified technique of dorsal plication for penile curvature with or without hypospadias. *Urology*, 2002. 59: 584.
<https://www.ncbi.nlm.nih.gov/pubmed/11927319>
361. Arafa, M., *et al.* The prevalence of Peyronie's disease in diabetic patients with erectile dysfunction. *Int J Impot Res*, 2007. 19: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/16915304>
362. Kumar, B., *et al.* A clinico-aetiological and ultrasonographic study of Peyronie's disease. *Sex Health*, 2006. 3: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/16800397>
363. La Pera, G., *et al.* Peyronie's disease: prevalence and association with cigarette smoking. A multicenter population-based study in men aged 50-69 years. *Eur Urol*, 2001. 40: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/11752860>
364. Lindsay, M.B., *et al.* The incidence of Peyronie's disease in Rochester, Minnesota, 1950 through 1984. *J Urol*, 1991. 146: 1007.
<https://www.ncbi.nlm.nih.gov/pubmed/1895413>
365. Mulhall, J.P., *et al.* Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. *J Urol*, 2004. 171: 2350.
<https://www.ncbi.nlm.nih.gov/pubmed/15126819>

366. Rhoden, E.L., *et al.* Prevalence of Peyronie's disease in men over 50-y-old from Southern Brazil. *Int J Impot Res*, 2001. 13: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/11890516>
367. Schwarzer, U., *et al.* The prevalence of Peyronie's disease: results of a large survey. *BJU Int*, 2001. 88: 727.
<https://www.ncbi.nlm.nih.gov/pubmed/11890244>
368. Sommer, F., *et al.* Epidemiology of Peyronie's disease. *Int J Impot Res*, 2002. 14: 379.
<https://www.ncbi.nlm.nih.gov/pubmed/12454689>
369. Stuntz, M., *et al.* The Prevalence of Peyronie's Disease in the United States: A Population-Based Study. *PLoS One*, 2016. 11: e0150157.
<https://www.ncbi.nlm.nih.gov/pubmed/26907743>
370. Devine, C.J., Jr., *et al.* Proposal: trauma as the cause of the Peyronie's lesion. *J Urol*, 1997. 157: 285.
<https://www.ncbi.nlm.nih.gov/pubmed/26907743>
371. Gonzalez-Cadavid, N.F., *et al.* Mechanisms of Disease: new insights into the cellular and molecular pathology of Peyronie's disease. *Nat Clin Pract Urol*, 2005. 2: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/16474811>
372. Jarow, J.P., *et al.* Penile trauma: an etiologic factor in Peyronie's disease and erectile dysfunction. *J Urol*, 1997. 158: 1388.
<https://www.ncbi.nlm.nih.gov/pubmed/9302127>
373. Kadioglu, A., *et al.* A retrospective review of 307 men with Peyronie's disease. *J Urol*, 2002. 168: 1075.
<https://www.ncbi.nlm.nih.gov/pubmed/12187226>
374. Rhoden, E.L., *et al.* A cross-sectional study for the analysis of clinical, sexual and laboratory conditions associated to Peyronie's disease. *J Sex Med*, 2010. 7: 1529.
<https://www.ncbi.nlm.nih.gov/pubmed/19912489>
375. Bjekic, M.D., *et al.* Risk factors for Peyronie's disease: a case-control study. *BJU Int*, 2006. 97: 570.
<https://www.ncbi.nlm.nih.gov/pubmed/16469028>
376. Carrieri, M.P., *et al.* A case-control study on risk factors for Peyronie's disease. *J Clin Epidemiol*, 1998. 51: 511.
<https://www.ncbi.nlm.nih.gov/pubmed/9636000>
377. Deveci, S., *et al.* Defining the clinical characteristics of Peyronie's disease in young men. *J Sex Med*, 2007. 4: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/17081219>
378. Ralph, D., *et al.* The management of Peyronie's disease: evidence-based 2010 guidelines. *J Sex Med*, 2010. 7: 2359.
<https://www.ncbi.nlm.nih.gov/pubmed/20497306>
379. Gelbard, M.K., *et al.* The natural history of Peyronie's disease. *J Urol*, 1990. 144: 1376.
<https://www.ncbi.nlm.nih.gov/pubmed/2231932>
380. Mulhall, J.P., *et al.* An analysis of the natural history of Peyronie's disease. *J Urol*, 2006. 175: 2115.
<https://www.ncbi.nlm.nih.gov/pubmed/16697815>
381. Pryor, J.P., *et al.* Clinical presentations of Peyronie's disease. *Int J Impot Res*, 2002. 14: 414.
<https://www.ncbi.nlm.nih.gov/pubmed/12454695>
382. Nelson, C.J., *et al.* The chronology of depression and distress in men with Peyronie's disease. *J Sex Med*, 2008. 5: 1985.
<https://www.ncbi.nlm.nih.gov/pubmed/18554257>
383. Hellstrom, W.J., *et al.* Bother and distress associated with Peyronie's disease: validation of the Peyronie's disease questionnaire. *J Urol*, 2013. 190: 627.
<https://www.ncbi.nlm.nih.gov/pubmed/23376705>
384. Hellstrom, W.J., *et al.* Self-report and Clinical Response to Peyronie's Disease Treatment: Peyronie's Disease Questionnaire Results From 2 Large Double-Blind, Randomized, Placebo-Controlled Phase 3 Studies. *Urology*, 2015. 86: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/26199168>
385. Bekos, A., *et al.* The natural history of Peyronie's disease: an ultrasonography-based study. *Eur Urol*, 2008. 53: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/17673362>
386. Greenfield, J.M., *et al.* Factors affecting the loss of length associated with tunica albuginea plication for correction of penile curvature. *J Urol*, 2006. 175: 238.
<https://www.ncbi.nlm.nih.gov/pubmed/16406919>

387. Levine, L.A., *et al.* Establishing a standardized evaluation of the man with Peyronie's disease. *Int J Impot Res*, 2003. 15 Suppl 5: S103.
<https://www.ncbi.nlm.nih.gov/pubmed/14551586>
388. Kadioglu, A., *et al.* Color Doppler ultrasound assessment of penile vascular system in men with Peyronie's disease. *Int J Impot Res*, 2000. 12: 263.
<https://www.ncbi.nlm.nih.gov/pubmed/11424963>
389. Porst, H., *et al.* Standards for clinical trials in male sexual dysfunctions. *J Sex Med*, 2010. 7: 414.
<https://www.ncbi.nlm.nih.gov/pubmed/20092447>
390. Hellstrom, W.J., *et al.* Peyronie's disease: etiology, medical, and surgical therapy. *J Androl*, 2000. 21: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/10819440>
391. Muller, A., *et al.* Peyronie's disease intervention trials: methodological challenges and issues. *J Sex Med*, 2009. 6: 848.
<https://www.ncbi.nlm.nih.gov/pubmed/19138374>
392. Shindel, A.W., *et al.* Urologist practice patterns in the management of Peyronie's disease: a nationwide survey. *J Sex Med*, 2008. 5: 954.
<https://www.ncbi.nlm.nih.gov/pubmed/18042214>
393. Pryor, J., *et al.* Controlled clinical trial of Vitamin E in Peyronie's disease. *Prog Reprod Biol*, 1983. 9.
[http://www.jsm.jsexmed.org/article/S1743-6095\(15\)30053-9/fulltext](http://www.jsm.jsexmed.org/article/S1743-6095(15)30053-9/fulltext)
394. Abner, E.L., *et al.* Vitamin E and all-cause mortality: a meta-analysis. *Curr Aging Sci*, 2011. 4: 158.
<https://www.ncbi.nlm.nih.gov/pubmed/21235492>
395. Griffiths, M.R., *et al.* A comparison of morphea and lichen sclerosus et atrophicus in vitro: the effects of para-aminobenzoate on skin fibroblasts. *Acta Derm Venereol*, 1992. 72: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/1350132>
396. Zarafonitis, C.J., *et al.* Treatment of Peyronie's disease with potassium para-aminobenzoate (potaba). *J Urol*, 1959. 81: 770.
<https://www.ncbi.nlm.nih.gov/pubmed/13655401>
397. Shah, P., *et al.* A multicentre double-blind controlled clinical trial of potassium para-amino-benzoate (POTABA1) in Peyronie's disease. *Progr Reprod Biol Med*, 1983. 9. [No abstract available].
398. Weidner, W., *et al.* Potassium paraaminobenzoate (POTABA) in the treatment of Peyronie's disease: a prospective, placebo-controlled, randomized study. *Eur Urol*, 2005. 47: 530.
<https://www.ncbi.nlm.nih.gov/pubmed/15774254>
399. Gur, S., *et al.* Current status and new developments in Peyronie's disease: medical, minimally invasive and surgical treatment options. *Expert Opin Pharmacother*, 2011. 12: 931.
<https://www.ncbi.nlm.nih.gov/pubmed/21405946>
400. Ralph, D.J., *et al.* The treatment of Peyronie's disease with tamoxifen. *Br J Urol*, 1992. 70: 648.
<https://www.ncbi.nlm.nih.gov/pubmed/1486392>
401. Teloken, C., *et al.* Tamoxifen versus placebo in the treatment of Peyronie's disease. *J Urol*, 1999. 162: 2003.
<https://www.ncbi.nlm.nih.gov/pubmed/10569556>
402. Kadioglu, A., *et al.* Treatment of Peyronie's disease with oral colchicine: long-term results and predictive parameters of successful outcome. *Int J Impot Res*, 2000. 12: 169.
<https://www.ncbi.nlm.nih.gov/pubmed/11045911>
403. Akkus, E., *et al.* Is colchicine effective in Peyronie's disease? A pilot study. *Urology*, 1994. 44: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/8048212>
404. Akman, T., *et al.* The most commonly altered type of Peyronie's disease deformity under oral colchicine treatment is lateral curvature that mostly shifts to the dorsal side. *Andrologia*, 2011. 43: 28.
<https://www.ncbi.nlm.nih.gov/pubmed/21219379>
405. Prieto Castro, R.M., *et al.* Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. *BJU Int*, 2003. 91: 522.
<https://www.ncbi.nlm.nih.gov/pubmed/12656907>
406. Biagiotti, G., *et al.* Acetyl-L-carnitine vs tamoxifen in the oral therapy of Peyronie's disease: a preliminary report. *BJU Int*, 2001. 88: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/11446848>
407. Cavallini, G., *et al.* Oral propionyl-L-carnitine and intraplaque verapamil in the therapy of advanced and resistant Peyronie's disease. *BJU Int*, 2002. 89: 895.
<https://www.ncbi.nlm.nih.gov/pubmed/12010235>

408. Shindel, A.W., *et al.* Pentoxifylline attenuates transforming growth factor-beta1-stimulated collagen deposition and elastogenesis in human tunica albuginea-derived fibroblasts part 1: impact on extracellular matrix. *J Sex Med*, 2010. 7: 2077.
<https://www.ncbi.nlm.nih.gov/pubmed/12010235>
409. Brant, W.O., *et al.* Treatment of Peyronie's disease with oral pentoxifylline. *Nat Clin Pract Urol*, 2006. 3: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/16470210>
410. Smith, J.F., *et al.* Pentoxifylline treatment and penile calcifications in men with Peyronie's disease. *Asian J Androl*, 2011. 13: 322.
<https://www.ncbi.nlm.nih.gov/pubmed/21102473>
411. Ferrini, M.G., *et al.* Effects of long-term vardenafil treatment on the development of fibrotic plaques in a rat model of Peyronie's disease. *BJU Int*, 2006. 97: 625.
<https://www.ncbi.nlm.nih.gov/pubmed/16469038>
412. Chung, E., *et al.* The role of PDE5 inhibitors in penile septal scar remodeling: assessment of clinical and radiological outcomes. *J Sex Med*, 2011. 8: 1472.
<https://www.ncbi.nlm.nih.gov/pubmed/21324095>
413. Tranchant, C., *et al.* [Mechanism of action of glucocorticoids: role of lipocortins]. *Rev Neurol (Paris)*, 1989. 145: 813.
<https://www.ncbi.nlm.nih.gov/pubmed/2533385>
414. Desanctis, P.N., *et al.* Steroid injection therapy for Peyronie's disease: a 10-year summary and review of 38 cases. *J Urol*, 1967. 97: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/6016195>
415. Winter, C.C., *et al.* Peyronie's disease: results with dermo-jet injection of dexamethasone. *J Urol*, 1975. 114: 898.
<https://www.ncbi.nlm.nih.gov/pubmed/1195471>
416. Cipollone, G., *et al.* [Betamethasone versus placebo in Peyronie's disease]. *Arch Ital Urol Androl*, 1998. 70: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/9823662>
417. Mulhall, J.P., *et al.* Peyronie's disease cell culture models: phenotypic, genotypic and functional analyses. *Int J Impot Res*, 2002. 14: 397.
<https://www.ncbi.nlm.nih.gov/pubmed/12454692>
418. Roth, M., *et al.* Ca²⁺ channel blockers modulate metabolism of collagens within the extracellular matrix. *Proc Natl Acad Sci U S A*, 1996. 93: 5478.
<https://www.ncbi.nlm.nih.gov/pubmed/8643600>
419. Anderson, M.S., *et al.* Inhibition of Peyronie's plaque fibroblast proliferation by biologic agents. *Int J Impot Res*, 2000. 12 Suppl 3: S25.
<https://www.ncbi.nlm.nih.gov/pubmed/11002396>
420. Bennett, N.E., *et al.* Intralesional verapamil prevents the progression of Peyronie's disease. *Urology*, 2007. 69: 1181.
<https://www.ncbi.nlm.nih.gov/pubmed/17572211>
421. Cavallini, G., *et al.* Open preliminary randomized prospective clinical trial of efficacy and safety of three different verapamil dilutions for intraplaque therapy of Peyronie's disease. *Urology*, 2007. 69: 950.
<https://www.ncbi.nlm.nih.gov/pubmed/17482941>
422. Levine, L.A., *et al.* Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol*, 2002. 168: 621.
<https://www.ncbi.nlm.nih.gov/pubmed/12131321>
423. Rehman, J., *et al.* Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. *Urology*, 1998. 51: 620.
<https://www.ncbi.nlm.nih.gov/pubmed/9586617>
424. Shirazi, M., *et al.* Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. *Int Urol Nephrol*, 2009. 41: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/19199072>
425. Moskovic, D.J., *et al.* Defining predictors of response to intralesional verapamil injection therapy for Peyronie's disease. *BJU Int*, 2011. 108: 1485.
<https://www.ncbi.nlm.nih.gov/pubmed/21733073>
426. Ehrlich, H.P. Scar contracture: cellular and connective tissue aspects in Peyronie's disease. *J Urol*, 1997. 157: 316.
<https://www.ncbi.nlm.nih.gov/pubmed/8976288>

427. Gelbard, M.K., *et al.* Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. *J Urol*, 1993. 149: 56.
<https://www.ncbi.nlm.nih.gov/pubmed/8976288>
428. Jordan, G.H. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. *J Sex Med*, 2008. 5: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/18173766>
429. Lipshultz, L.I., *et al.* Clinical efficacy of collagenase *Clostridium histolyticum* in the treatment of Peyronie's disease by subgroup: results from two large, double-blind, randomized, placebo-controlled, phase III studies. *BJU Int*, 2015. 116: 650.
<https://www.ncbi.nlm.nih.gov/pubmed/25711400>
430. EMA, *et al.* Assessment Report - Xiapex (Collagenase *Clostridium Histolyticum*). 2014.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002048/WC500187327.pdf
431. Carson, C.C., 3rd, *et al.* Analysis of the clinical safety of intralesional injection of collagenase *Clostridium histolyticum* (CCH) for adults with Peyronie's disease (PD). *BJU Int*, 2015. 116: 815.
<https://www.ncbi.nlm.nih.gov/pubmed/25818264>
432. Duncan, M.R., *et al.* Regulation of the proliferation and biosynthetic activities of cultured human Peyronie's disease fibroblasts by interferons-alpha, -beta and -gamma. *Scand J Urol Nephrol*, 1991. 25: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/1651559>
433. Hellstrom, W.J., *et al.* Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. *J Urol*, 2006. 176: 394.
<https://www.ncbi.nlm.nih.gov/pubmed/16753449>
434. Kendirci, M., *et al.* The impact of intralesional interferon alpha-2b injection therapy on penile hemodynamics in men with Peyronie's disease. *J Sex Med*, 2005. 2: 709.
<https://www.ncbi.nlm.nih.gov/pubmed/16422829>
435. Zucchi, A., *et al.* Intralesional Injection of Hyaluronic Acid in Patients Affected With Peyronie's Disease: Preliminary Results From a Prospective, Multicenter, Pilot Study. *Sex Med*, 2016. 4: e83.
<https://www.ncbi.nlm.nih.gov/pubmed/26984291>
436. Martin, D.J., *et al.* Transdermal application of verapamil gel to the penile shaft fails to infiltrate the tunica albuginea. *J Urol*, 2002. 168: 2483.
<https://www.ncbi.nlm.nih.gov/pubmed/12441945>
437. Di Stasi, S.M., *et al.* Transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *BJU Int*, 2003. 91: 825.
<https://www.ncbi.nlm.nih.gov/pubmed/12780842>
438. Greenfield, J.M., *et al.* Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol*, 2007. 177: 972.
<https://www.ncbi.nlm.nih.gov/pubmed/17296390>
439. Twidwell, J., *et al.* Topical treatment for acute phase Peyronie's disease utilizing a new gel, H-100: a randomized, prospective, placebo-controlled pilot study. *Int J Impot Res*, 2016. 28: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/26700214>
440. Husain, J., *et al.* Extracorporeal shock wave therapy in the management of Peyronie's disease: initial experience. *BJU Int*, 2000. 86: 466.
<https://www.ncbi.nlm.nih.gov/pubmed/10971273>
441. Hauck, E.W., *et al.* Questionable efficacy of extracorporeal shock wave therapy for Peyronie's disease: results of a prospective approach. *J Urol*, 2004. 171: 296.
<https://www.ncbi.nlm.nih.gov/pubmed/14665898>
442. Srirangam, S.J., *et al.* Long-term results of extracorporeal shockwave therapy for Peyronie's disease. *J Endourol*, 2006. 20: 880.
<https://www.ncbi.nlm.nih.gov/pubmed/17144855>
443. Strebel, R.T., *et al.* Extracorporeal shockwave therapy for Peyronie's disease does not correct penile deformity. *Int J Impot Res*, 2004. 16: 448.
<https://www.ncbi.nlm.nih.gov/pubmed/14973523>
444. Palmieri, A., *et al.* A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. *Eur Urol*, 2009. 56: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/19473751>

445. Bailey, A.J., *et al.* The continuous elongation technique for severe Dupuytren's disease. A biochemical mechanism. *J Hand Surg Br*, 1994. 19: 522.
<https://www.ncbi.nlm.nih.gov/pubmed/19473751>
446. Martinez-Salamanca, J.I., *et al.* Acute phase Peyronie's disease management with traction device: a nonrandomized prospective controlled trial with ultrasound correlation. *J Sex Med*, 2014. 11: 506.
<https://www.ncbi.nlm.nih.gov/pubmed/24261900>
447. Kendirci, M., *et al.* Critical analysis of surgery for Peyronie's disease. *Curr Opin Urol*, 2004. 14: 381.
<https://www.ncbi.nlm.nih.gov/pubmed/15626883>
448. Langston, J.P., *et al.* Peyronie disease: plication or grafting. *Urol Clin North Am*, 2011. 38: 207.
<https://www.ncbi.nlm.nih.gov/pubmed/21621087>
449. Garaffa, G., *et al.* Circumcision is not mandatory in penile surgery. *BJU Int*, 2010. 105: 222.
<https://www.ncbi.nlm.nih.gov/pubmed/19594732>
450. Mulhall, J., *et al.* A surgical algorithm for men with combined Peyronie's disease and erectile dysfunction: functional and satisfaction outcomes. *J Sex Med*, 2005. 2: 132.
<https://www.ncbi.nlm.nih.gov/pubmed/16422916>
451. Smith, J.F., *et al.* Peyronie's disease: a critical appraisal of current diagnosis and treatment. *Int J Impot Res*, 2008. 20: 445.
<https://www.ncbi.nlm.nih.gov/pubmed/18650828>
452. Nesbit, R.M. Congenital curvature of the phallus: report of three cases with description of corrective operation. *J Urol*, 1965. 93: 230.
<https://www.ncbi.nlm.nih.gov/pubmed/14260875>
453. Pryor, J.P., *et al.* A new approach to the correction of the penile deformity in Peyronie's disease. *J Urol*, 1979. 122: 622.
<https://www.ncbi.nlm.nih.gov/pubmed/501814>
454. Pryor, J.P. Correction of penile curvature and Peyronie's disease: why I prefer the Nesbit technique. *Int J Impot Res*, 1998. 10: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/9647952>
455. Ralph, D.J., *et al.* The Nesbit operation for Peyronie's disease: 16-year experience. *J Urol*, 1995. 154: 1362.
<https://www.ncbi.nlm.nih.gov/pubmed/7658538>
456. Savoca, G., *et al.* Long-term results with Nesbit's procedure as treatment of Peyronie's disease. *Int J Impot Res*, 2000. 12: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/11424968>
457. Rehman, J., *et al.* Results of surgical treatment for abnormal penile curvature: Peyronie's disease and congenital deviation by modified Nesbit plication (tunical shaving and plication). *J Urol*, 1997. 157: 1288.
<https://www.ncbi.nlm.nih.gov/pubmed/9120923>
458. Ebbehøj, J., *et al.* New operation for "krummerik" (penile curvature). *Urology*, 1985. 26: 76.
<https://www.ncbi.nlm.nih.gov/pubmed/3892851>
459. Essed, E., *et al.* New surgical treatment for Peyronie disease. *Urology*, 1985. 25: 582.
<https://www.ncbi.nlm.nih.gov/pubmed/4012950>
460. Lemberger, R.J., *et al.* Nesbit's operation for Peyronie's disease. *Br J Urol*, 1984. 56: 721.
<https://www.ncbi.nlm.nih.gov/pubmed/6534497>
461. Licht, M.R., *et al.* Modified Nesbit procedure for the treatment of Peyronie's disease: a comparative outcome analysis. *J Urol*, 1997. 158: 460.
<https://www.ncbi.nlm.nih.gov/pubmed/9224323>
462. Sassine, A.M., *et al.* Modified corporoplasty for penile curvature: 10 years' experience. *Urology*, 1994. 44: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/8073558>
463. Yachia, D. Modified corporoplasty for the treatment of penile curvature. *J Urol*, 1990. 143: 80.
<https://www.ncbi.nlm.nih.gov/pubmed/2294269>
464. Gholami, S.S., *et al.* Correction of penile curvature using the 16-dot plication technique: a review of 132 patients. *J Urol*, 2002. 167: 2066.
<https://www.ncbi.nlm.nih.gov/pubmed/11956440>
465. Dalkin, B.L., *et al.* Venogenic impotence following dermal graft repair for Peyronie's disease. *J Urol*, 1991. 146: 849.
<https://www.ncbi.nlm.nih.gov/pubmed/1843616>
466. Devine, C.J., Jr., *et al.* Surgical treatment of Peyronie's disease with a dermal graft. *J Urol*, 1974. 111: 44.
<https://www.ncbi.nlm.nih.gov/pubmed/4273261>

467. Bokarica, P., *et al.* Surgical treatment of Peyronie's disease based on penile length and degree of curvature. *Int J Impot Res*, 2005. 17: 170.
<https://www.ncbi.nlm.nih.gov/pubmed/15215882>
468. Burnett, A.L. Fascia lata in penile reconstructive surgery: a reappraisal of the fascia lata graft. *Plast Reconstr Surg*, 1997. 99: 1061.
<https://www.ncbi.nlm.nih.gov/pubmed/9091903>
469. Cormio, L., *et al.* Surgical treatment of Peyronie's disease by plaque incision and grafting with buccal mucosa. *Eur Urol*, 2009. 55: 1469.
<https://www.ncbi.nlm.nih.gov/pubmed/19084325>
470. Das, S. Peyronie's disease: excision and autografting with tunica vaginalis. *J Urol*, 1980. 124: 818.
<https://www.ncbi.nlm.nih.gov/pubmed/7441830>
471. Egydio, P.H., *et al.* A single relaxing incision to correct different types of penile curvature: surgical technique based on geometrical principles. *BJU Int*, 2004. 94: 1147.
<https://www.ncbi.nlm.nih.gov/pubmed/15541152>
472. El-Sakka, A.I., *et al.* Venous patch graft for Peyronie's disease. Part II: outcome analysis. *J Urol*, 1998. 160: 2050.
<https://www.ncbi.nlm.nih.gov/pubmed/9817321>
473. Faerber, G.J., *et al.* Results of combined Nesbit penile plication with plaque incision and placement of Dacron patch in patients with severe Peyronie's disease. *J Urol*, 1993. 149: 1319.
<https://www.ncbi.nlm.nih.gov/pubmed/8479026>
474. Fallon, B. Cadaveric dura mater graft for correction of penile curvature in Peyronie disease. *Urology*, 1990. 35: 127.
<https://www.ncbi.nlm.nih.gov/pubmed/2305535>
475. Gelbard, M.K., *et al.* Expanding contractures of the tunica albuginea due to Peyronie's disease with temporalis fascia free grafts. *J Urol*, 1991. 145: 772.
<https://www.ncbi.nlm.nih.gov/pubmed/2005698>
476. Hatzichristou, D.G., *et al.* Corporoplasty using tunica albuginea free grafts for penile curvature: surgical technique and long-term results. *J Urol*, 2002. 167: 1367.
<https://www.ncbi.nlm.nih.gov/pubmed/11832734>
477. Kadioglu, A., *et al.* Surgical treatment of Peyronie's disease with incision and venous patch technique. *Int J Impot Res*, 1999. 11: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/10356666>
478. Knoll, L.D. Use of porcine small intestinal submucosal graft in the surgical management of Peyronie's disease. *Urology*, 2001. 57: 753.
<https://www.ncbi.nlm.nih.gov/pubmed/11306396>
479. Leungwattanakij, S., *et al.* Comparison of cadaveric pericardial, dermal, vein, and synthetic grafts for tunica albuginea substitution using a rat model. *BJU Int*, 2003. 92: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/12823395>
480. Montorsi, F., *et al.* Evidence based assessment of long-term results of plaque incision and vein grafting for Peyronie's disease. *J Urol*, 2000. 163: 1704.
<https://www.ncbi.nlm.nih.gov/pubmed/10799165>
481. Taylor, F.L., *et al.* Surgical correction of Peyronie's disease via tunica albuginea plication or partial plaque excision with pericardial graft: long-term follow up. *J Sex Med*, 2008. 5: 2221.
<https://www.ncbi.nlm.nih.gov/pubmed/18637996>
482. Kadioglu, A., *et al.* Surgical treatment of Peyronie's disease: a critical analysis. *Eur Urol*, 2006. 50: 235.
<https://www.ncbi.nlm.nih.gov/pubmed/16716495>
483. Chun, J.L., *et al.* A comparison of dermal and cadaveric pericardial grafts in the modified Horton-Devine procedure for Peyronie's disease. *J Urol*, 2001. 166: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/11435853>
484. Hatzichristodoulou, G., *et al.* Surgical therapy of Peyronie's disease by partial plaque excision and grafting with collagen fleece: feasibility study of a new technique. *Int J Impot Res*, 2013. 25: 183.
<https://www.ncbi.nlm.nih.gov/pubmed/23446807>
485. Chung, E., *et al.* Five-year follow-up of Peyronie's graft surgery: outcomes and patient satisfaction. *J Sex Med*, 2011. 8: 594.
<https://www.ncbi.nlm.nih.gov/pubmed/21054805>
486. Taylor, F.L., *et al.* Peyronie's Disease. *Urol Clin North Am*, 2007. 34: 517.
<https://www.ncbi.nlm.nih.gov/pubmed/17983892>
487. Wilson, S.K. Surgical techniques: modeling technique for penile curvature. *J Sex Med*, 2007. 4: 231.
<https://www.ncbi.nlm.nih.gov/pubmed/17233788>

488. Wilson, S.K., *et al.* A new treatment for Peyronie's disease: modeling the penis over an inflatable penile prosthesis. *J Urol*, 1994. 152: 1121.
<https://www.ncbi.nlm.nih.gov/pubmed/8072079>
489. Montague, D.K., *et al.* AMS 3-piece inflatable penile prosthesis implantation in men with Peyronie's disease: comparison of CX and Ultrex cylinders. *J Urol*, 1996. 156: 1633.
<https://www.ncbi.nlm.nih.gov/pubmed/8863557>
490. Carson, C.C. Penile prosthesis implantation in the treatment of Peyronie's disease. *Int J Impot Res*, 1998. 10: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/9647951>
491. Chaudhary, M., *et al.* Peyronie's disease with erectile dysfunction: penile modeling over inflatable penile prostheses. *Urology*, 2005. 65: 760.
<https://www.ncbi.nlm.nih.gov/pubmed/15833523>
492. Rolle, L., *et al.* A prospective multicentric international study on the surgical outcomes and patients' satisfaction rates of the 'sliding' technique for end-stage Peyronie's disease with severe shortening of the penis and erectile dysfunction. *BJU Int*, 2016. 117: 814.
<https://www.ncbi.nlm.nih.gov/pubmed/26688436>
493. Berger, R., *et al.* Report of the American Foundation for Urologic Disease (AFUD) Thought Leader Panel for evaluation and treatment of priapism. *Int J Impot Res*, 2001. 13 Suppl 5: S39.
<https://www.ncbi.nlm.nih.gov/pubmed/11781746>
494. Broderick, G.A., *et al.* Priapism: pathogenesis, epidemiology, and management. *J Sex Med*, 2010. 7: 476.
<https://www.ncbi.nlm.nih.gov/pubmed/20092449>
495. Muneer, A., *et al.* Investigation of cavernosal smooth muscle dysfunction in low flow priapism using an in vitro model. *Int J Impot Res*, 2005. 17: 10.
<https://www.ncbi.nlm.nih.gov/pubmed/15071490>
496. El-Bahnasawy, M.S., *et al.* Low-flow priapism: risk factors for erectile dysfunction. *BJU Int*, 2002. 89: 285.
<https://www.ncbi.nlm.nih.gov/pubmed/11856112>
497. Spycher, M.A., *et al.* The ultrastructure of the erectile tissue in priapism. *J Urol*, 1986. 135: 142.
<https://www.ncbi.nlm.nih.gov/pubmed/3941454>
498. Pohl, J., *et al.* Priapism: a three-phase concept of management according to aetiology and prognosis. *Br J Urol*, 1986. 58: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/3516294>
499. Junemann, K.P., *et al.* Pathophysiology of erectile dysfunction. *Semin Urol*, 1990. 8: 80.
<https://www.ncbi.nlm.nih.gov/pubmed/2191403>
500. Porst, H. The rationale for prostaglandin E1 in erectile failure: a survey of worldwide experience. *J Urol*, 1996. 155: 802.
<https://www.ncbi.nlm.nih.gov/pubmed/8583582>
501. Nelson, J.H., 3rd, *et al.* Priapism: evolution of management in 48 patients in a 22-year series. *J Urol*, 1977. 117: 455.
<https://www.ncbi.nlm.nih.gov/pubmed/15137>
502. Ateyah, A., *et al.* Intracavernosal irrigation by cold saline as a simple method of treating iatrogenic prolonged erection. *J Sex Med*, 2005. 2: 248.
<https://www.ncbi.nlm.nih.gov/pubmed/16422893>
503. Bivalacqua, T.J., *et al.* New insights into the pathophysiology of sickle cell disease-associated priapism. *J Sex Med*, 2012. 9: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/21554553>
504. Lagoda, G., *et al.* Molecular analysis of erection regulatory factors in sickle cell disease associated priapism in the human penis. *J Urol*, 2013. 189: 762.
<https://www.ncbi.nlm.nih.gov/pubmed/22982429>
505. Alwaal, A., *et al.* Future prospects in the treatment of erectile dysfunction: focus on avanafil. *Drug Des Devel Ther*, 2011. 5: 435.
<https://www.ncbi.nlm.nih.gov/pubmed/22087063>
506. Kropman, R.F., *et al.* Hematoma or "partial priapism" in the proximal part of the corpus cavernosum. *J Sex Med*, 2014. 11: 2618.
<https://www.ncbi.nlm.nih.gov/pubmed/24308665>
507. Weyne, E., *et al.* Idiopathic Partial Thrombosis (IPT) of the Corpus Cavernosum: A Hypothesis-Generating Case Series and Review of the Literature. *J Sex Med*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26553854>

508. Burnett, A.L., *et al.* Priapism: new concepts in medical and surgical management. *Urol Clin North Am*, 2011. 38: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/21621085>
509. Broderick, G.A. Priapism and sickle-cell anemia: diagnosis and nonsurgical therapy. *J Sex Med*, 2012. 9: 88.
<https://www.ncbi.nlm.nih.gov/pubmed/21699659>
510. Bertolotto, M., *et al.* Color Doppler imaging of posttraumatic priapism before and after selective embolization. *Radiographics*, 2003. 23: 495.
<https://www.ncbi.nlm.nih.gov/pubmed/12640162>
511. Bertolotto, M., *et al.* Color Doppler appearance of penile cavernosal-spongiosal communications in patients with high-flow priapism. *Acta Radiol*, 2008. 49: 710.
<https://www.ncbi.nlm.nih.gov/pubmed/18568565>
512. Hakim, L.S., *et al.* Evolving concepts in the diagnosis and treatment of arterial high flow priapism. *J Urol*, 1996. 155: 541.
<https://www.ncbi.nlm.nih.gov/pubmed/8558656>
513. Bastuba, M.D., *et al.* Arterial priapism: diagnosis, treatment and long-term followup. *J Urol*, 1994. 151: 1231.
<https://www.ncbi.nlm.nih.gov/pubmed/8158765>
514. Ralph, D.J., *et al.* The use of high-resolution magnetic resonance imaging in the management of patients presenting with priapism. *BJU Int*, 2010. 106: 1714.
<https://www.ncbi.nlm.nih.gov/pubmed/20438564>
515. Hoyerup, P., *et al.* Partial priapism. *BMJ Case Rep*, 2013. 2013.
<https://www.ncbi.nlm.nih.gov/pubmed/23933863>
516. Burnett, A.L., *et al.* Standard operating procedures for priapism. *J Sex Med*, 2013. 10: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/23211057>
517. Bodner, D.R., *et al.* The application of intracavernous injection of vasoactive medications for erection in men with spinal cord injury. *J Urol*, 1987. 138: 310.
<https://www.ncbi.nlm.nih.gov/pubmed/3599245>
518. Davila, H.H., *et al.* Subarachnoid hemorrhage as complication of phenylephrine injection for the treatment of ischemic priapism in a sickle cell disease patient. *J Sex Med*, 2008. 5: 1025.
<https://www.ncbi.nlm.nih.gov/pubmed/18194188>
519. Mantadakis, E., *et al.* Outpatient penile aspiration and epinephrine irrigation for young patients with sickle cell anemia and prolonged priapism. *Blood*, 2000. 95: 78.
<https://www.ncbi.nlm.nih.gov/pubmed/10607688>
520. Miller, S.F., *et al.* Posttraumatic arterial priapism in children: management with embolization. *Radiology*, 1995. 196: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/7784590>
521. Munarriz, R., *et al.* Management of ischemic priapism with high-dose intracavernosal phenylephrine: from bench to bedside. *J Sex Med*, 2006. 3: 918.
<https://www.ncbi.nlm.nih.gov/pubmed/16942536>
522. Muneer, A., *et al.* Investigating the effects of high-dose phenylephrine in the management of prolonged ischaemic priapism. *J Sex Med*, 2008. 5: 2152.
<https://www.ncbi.nlm.nih.gov/pubmed/18466270>
523. Muruve, N., *et al.* Intracorporeal phenylephrine in the treatment of priapism. *J Urol*, 1996. 155: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/7490814>
524. Roberts, J.R., *et al.* Intracavernous epinephrine: a minimally invasive treatment for priapism in the emergency department. *J Emerg Med*, 2009. 36: 285.
<https://www.ncbi.nlm.nih.gov/pubmed/18996674>
525. Keskin, D., *et al.* Intracavernosal adrenalin injection in priapism. *Int J Impot Res*, 2000. 12: 312.
<https://www.ncbi.nlm.nih.gov/pubmed/11416834>
526. Hubler, J., *et al.* Methylene blue as a means of treatment for priapism caused by intracavernous injection to combat erectile dysfunction. *Int Urol Nephrol*, 2003. 35: 519.
<https://www.ncbi.nlm.nih.gov/pubmed/15198160>
527. Martinez Portillo, F., *et al.* Methylene blue as a successful treatment alternative for pharmacologically induced priapism. *Eur Urol*, 2001. 39: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/11173934>
528. Gupta, A., *et al.* Successful use of terbutaline in persistent priapism in a 12-year-old boy with chronic myeloid leukemia. *Pediatr Hematol Oncol*, 2009. 26: 70.
<https://www.ncbi.nlm.nih.gov/pubmed/19206011>

529. Lowe, F.C., *et al.* Placebo-controlled study of oral terbutaline and pseudoephedrine in management of prostaglandin E1-induced prolonged erections. *Urology*, 1993. 42: 51.
<https://www.ncbi.nlm.nih.gov/pubmed/8392235>
530. Priyadarshi, S. Oral terbutaline in the management of pharmacologically induced prolonged erection. *Int J Impot Res*, 2004. 16: 424.
<https://www.ncbi.nlm.nih.gov/pubmed/14999218>
531. Bartolucci, P., *et al.* Clinical management of adult sickle-cell disease. *Curr Opin Hematol*, 2012. 19: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/22357165>
532. Levey, H.R., *et al.* Medical management of ischemic stuttering priapism: a contemporary review of the literature. *Asian J Androl*, 2012. 14: 156.
<https://www.ncbi.nlm.nih.gov/pubmed/22057380>
533. Rogers, Z.R. Priapism in sickle cell disease. *Hematol Oncol Clin North Am*, 2005. 19: 917.
<https://www.ncbi.nlm.nih.gov/pubmed/16214652>
534. Morrison, B.F., *et al.* Priapism in hematological and coagulative disorders: an update. *Nat Rev Urol*, 2011. 8: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/21403660>
535. Ballas, S.K., *et al.* Safety and efficacy of blood exchange transfusion for priapism complicating sickle cell disease. *J Clin Apheresis*, 2016. 31: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/25809639>
536. Marouf, R. Blood transfusion in sickle cell disease. *Hemoglobin*, 2011. 35: 495.
<https://www.ncbi.nlm.nih.gov/pubmed/21981466>
537. Merritt, A.L., *et al.* Myth: blood transfusion is effective for sickle cell anemia-associated priapism. *CJEM*, 2006. 8: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/17175874>
538. Burnett, A.L. Surgical management of ischemic priapism. *J Sex Med*, 2012. 9: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/22221308>
539. Bennett, N., *et al.* Sickle cell disease status and outcomes of African-American men presenting with priapism. *J Sex Med*, 2008. 5: 1244.
<https://www.ncbi.nlm.nih.gov/pubmed/18312286>
540. Nixon, R.G., *et al.* Efficacy of shunt surgery for refractory low flow priapism: a report on the incidence of failed detumescence and erectile dysfunction. *J Urol*, 2003. 170: 883.
<https://www.ncbi.nlm.nih.gov/pubmed/12913722>
541. Zacharakis, E., *et al.* Penile prosthesis insertion in patients with refractory ischaemic priapism: early vs delayed implantation. *BJU Int*, 2014. 114: 576.
<https://www.ncbi.nlm.nih.gov/pubmed/25383397>
542. Zacharakis, E., *et al.* The efficacy of the T-shunt procedure and intracavernous tunneling (snake maneuver) for refractory ischemic priapism. *J Urol*, 2014. 191: 164.
<https://www.ncbi.nlm.nih.gov/pubmed/23892191>
543. Lue, T.F., *et al.* Distal cavernosum-glans shunts for ischemic priapism. *J Sex Med*, 2006. 3: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/16839333>
544. Winter, C.C. Cure of idiopathic priapism: new procedure for creating fistula between glans penis and corpora cavernosa. *Urology*, 1976. 8: 389.
<https://www.ncbi.nlm.nih.gov/pubmed/973296>
545. Macaluso, J.N., Jr., *et al.* Priapism: review of 34 cases. *Urology*, 1985. 26: 233.
<https://www.ncbi.nlm.nih.gov/pubmed/4035837>
546. Ebbehøj, J. A new operation for priapism. *Scand J Plast Reconstr Surg*, 1974. 8: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/4458048>
547. Lund, K., *et al.* Results of glando-cavernous anastomosis in 18 cases of priapism. *Scand J Plast Reconstr Surg*, 1980. 14: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/7209413>
548. Brant, W.O., *et al.* T-shaped shunt and intracavernous tunneling for prolonged ischemic priapism. *J Urol*, 2009. 181: 1699.
<https://www.ncbi.nlm.nih.gov/pubmed/19233430>
549. Ercole, C.J., *et al.* Changing surgical concepts in the treatment of priapism. *J Urol*, 1981. 125: 210.
<https://www.ncbi.nlm.nih.gov/pubmed/7206057>
550. Hanafy, H.M., *et al.* Ancient Egyptian medicine: contribution to urology. *Urology*, 1974. 4: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/21323001>

551. Burnett, A.L., *et al.* Corporal “snake” maneuver: corporoglanular shunt surgical modification for ischemic priapism. *J Sex Med*, 2009. 6: 1171.
<https://www.ncbi.nlm.nih.gov/pubmed/19207268>
552. Segal, R.L., *et al.* Corporal Burnett “Snake” surgical maneuver for the treatment of ischemic priapism: long-term followup. *J Urol*, 2013. 189: 1025.
<https://www.ncbi.nlm.nih.gov/pubmed/23017524>
553. Quackels, R. [Treatment of a case of priapism by cavernospongious anastomosis]. *Acta Urol Belg*, 1964. 32: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/14111379>
554. Grayhack, J.T., *et al.* Venous bypass to control priapism. *Invest Urol*, 1964. 1: 509.
<https://www.ncbi.nlm.nih.gov/pubmed/14130594>
555. Kandel, G.L., *et al.* Pulmonary embolism: a complication of corpus-saphenous shunt for priapism. *J Urol*, 1968. 99: 196.
<https://www.ncbi.nlm.nih.gov/pubmed/5641077>
556. Kihl, B., *et al.* Priapism: evaluation of treatment with special reference to saphenocavernous shunting in 26 patients. *Scand J Urol Nephrol*, 1980. 14: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/7375831>
557. Ralph, D.J., *et al.* The immediate insertion of a penile prosthesis for acute ischaemic priapism. *Eur Urol*, 2009. 56: 1033.
<https://www.ncbi.nlm.nih.gov/pubmed/18930579>
558. Salem, E.A., *et al.* Management of ischemic priapism by penile prosthesis insertion: prevention of distal erosion. *J Urol*, 2010. 183: 2300.
<https://www.ncbi.nlm.nih.gov/pubmed/20400140>
559. Sedigh, O., *et al.* Early insertion of inflatable prosthesis for intractable ischemic priapism: our experience and review of the literature. *Int J Impot Res*, 2011. 23: 158.
<https://www.ncbi.nlm.nih.gov/pubmed/21654814>
560. Upadhyay, J., *et al.* Penile implant for intractable priapism associated with sickle cell disease. *Urology*, 1998. 51: 638.
<https://www.ncbi.nlm.nih.gov/pubmed/9586621>
561. Zacharakis, E., *et al.* Early insertion of a malleable penile prosthesis in ischaemic priapism allows later upsizing of the cylinders. *Scan J Urol*, 2015. 26: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/26116193>
562. Burnett, A.L., *et al.* Evaluation of erectile function in men with sickle cell disease. *Urology*, 1995. 45: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/7716848>
563. Datta, N.S. Megalophallus in sickle cell disease. *J Urol*, 1977. 117: 672.
<https://www.ncbi.nlm.nih.gov/pubmed/859210>
564. Broderick, G.A., *et al.* Pharmacologic erection: time-dependent changes in the corporal environment. *Int J Impot Res*, 1994. 6: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/8019618>
565. Bertram, R.A., *et al.* Implantation of penile prostheses in patients impotent after priapism. *Urology*, 1985. 26: 325.
<https://www.ncbi.nlm.nih.gov/pubmed/4049609>
566. Monga, M., *et al.* Priapism in sickle cell disease: the case for early implantation of the penile prosthesis. *Eur Urol*, 1996. 30: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/8854068>
567. Hatzichristou, D., *et al.* Management strategy for arterial priapism: therapeutic dilemmas. *J Urol*, 2002. 168: 2074.
<https://www.ncbi.nlm.nih.gov/pubmed/12394712>
568. Witt, M.A., *et al.* Traumatic laceration of intracavernosal arteries: the pathophysiology of nonischemic, high flow, arterial priapism. *J Urol*, 1990. 143: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/2294241>
569. Kuefer, R., *et al.* Changing diagnostic and therapeutic concepts in high-flow priapism. *Int J Impot Res*, 2005. 17: 109.
<https://www.ncbi.nlm.nih.gov/pubmed/15229624>
570. Steers, W.D., *et al.* Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol*, 1991. 146: 1361.
<https://www.ncbi.nlm.nih.gov/pubmed/1942293>

571. Ricciardi, R., Jr., *et al.* Delayed high flow priapism: pathophysiology and management. *J Urol*, 1993. 149: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/8417190>
572. Dubocq, F.M., *et al.* High flow malignant priapism with isolated metastasis to the corpora cavernosa. *Urology*, 1998. 51: 324.
<https://www.ncbi.nlm.nih.gov/pubmed/9495721>
573. Inamoto, T., *et al.* A rare case of penile metastasis of testicular cancer presented with priapism. *Hinyokika Kyo*, 2005. 51: 639.
<https://www.ncbi.nlm.nih.gov/pubmed/16229380>
574. Todd, N.V. Priapism in acute spinal cord injury. *Spinal Cord*, 2011. 49: 1033.
<https://www.ncbi.nlm.nih.gov/pubmed/21647168>
575. Lutz, A., *et al.* Conversion of low-flow to high-flow priapism: a case report and review (CME). *J Sex Med*, 2012. 9: 951.
<https://www.ncbi.nlm.nih.gov/pubmed/22462585>
576. McMahon, C.G. High flow priapism due to an arterial-lacunar fistula complicating initial veno-occlusive priapism. *Int J Impot Res*, 2002. 14: 195.
<https://www.ncbi.nlm.nih.gov/pubmed/12058247>
577. Karagiannis, A.A., *et al.* High flow priapism secondary to internal urethrotomy treated with embolization. *J Urol*, 2004. 171: 1631.
<https://www.ncbi.nlm.nih.gov/pubmed/15017242>
578. Liguori, G., *et al.* High-flow priapism (HFP) secondary to Nesbit operation: management by percutaneous embolization and colour Doppler-guided compression. *Int J Impot Res*, 2005. 17: 304.
<https://www.ncbi.nlm.nih.gov/pubmed/15690066>
579. Ramos, C.E., *et al.* High flow priapism associated with sickle cell disease. *J Urol*, 1995. 153: 1619.
<https://www.ncbi.nlm.nih.gov/pubmed/7714988>
580. Kang, B.C., *et al.* Post-traumatic arterial priapism: colour Doppler examination and superselective arterial embolization. *Clin Radiol*, 1998. 53: 830.
<https://www.ncbi.nlm.nih.gov/pubmed/9833787>
581. Kolbenstedt, A., *et al.* Arterial high flow priapism role of radiology in diagnosis and treatment. *Scand J Urol Nephrol Suppl*, 1996. 179: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/8908681>
582. Eracleous, E., *et al.* Use of Doppler ultrasound and 3-dimensional contrast-enhanced MR angiography in the diagnosis and follow-up of post-traumatic high-flow priapism in a child. *Pediatr Radiol*, 2000. 30: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/10789908>
583. Arango, O., *et al.* Complete resolution of post-traumatic high-flow priapism with conservative treatment. *Int J Impot Res*, 1999. 11: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/10356672>
584. Ilkay, A.K., *et al.* Conservative management of high-flow priapism. *Urology*, 1995. 46: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/7660524>
585. Corbetta, J.P., *et al.* High flow priapism: diagnosis and treatment in pediatric population. *Pediatr Surg Int*, 2011. 27: 1217.
<https://www.ncbi.nlm.nih.gov/pubmed/21544645>
586. Mwamukonda, K.B., *et al.* Androgen blockade for the treatment of high-flow priapism. *J Sex Med*, 2010. 7: 2532.
<https://www.ncbi.nlm.nih.gov/pubmed/20456623>
587. Cakan, M., *et al.* Is the combination of superselective transcatheter autologous clot embolization and duplex sonography-guided compression therapy useful treatment option for the patients with high-flow priapism? *Int J Impot Res*, 2006. 18: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/16079900>
588. Kim, K.R., *et al.* Treatment of high-flow priapism with superselective transcatheter embolization in 27 patients: a multicenter study. *J Vasc Interv Radiol*, 2007. 18: 1222.
<https://www.ncbi.nlm.nih.gov/pubmed/17911511>
589. Numan, F., *et al.* Posttraumatic nonischemic priapism treated with autologous blood clot embolization. *J Sex Med*, 2008. 5: 173.
<https://www.ncbi.nlm.nih.gov/pubmed/18173765>
590. Gorich, J., *et al.* Interventional treatment of traumatic priapism. *J Endovasc Ther*, 2002. 9: 614.
<https://www.ncbi.nlm.nih.gov/pubmed/12431145>

591. Kerlan, R.K., Jr., *et al.* Superselective microcoil embolization in the management of high-flow priapism. *J Vasc Interv Radiol*, 1998. 9: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/9468400>
592. Liu, B.X., *et al.* High-flow priapism: superselective cavernous artery embolization with microcoils. *Urology*, 2008. 72: 571.
<https://www.ncbi.nlm.nih.gov/pubmed/18619653>
593. Numan, F., *et al.* Posttraumatic high-flow priapism treated by N-butyl-cyanoacrylate embolization. *Cardiovasc Intervent Radiol*, 1996. 19: 278.
<https://www.ncbi.nlm.nih.gov/pubmed/8755084>
594. Pryor, J., *et al.* Priapism. *J Sex Med*, 2004. 1: 116.
<https://www.ncbi.nlm.nih.gov/pubmed/16422992>
595. Sandock, D.S., *et al.* Perineal abscess after embolization for high-flow priapism. *Urology*, 1996. 48: 308.
<https://www.ncbi.nlm.nih.gov/pubmed/8753749>
596. Savoca, G., *et al.* Sexual function after highly selective embolization of cavernous artery in patients with high flow priapism: long-term followup. *J Urol*, 2004. 172: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/15247752>
597. Alexander Tonseth, K., *et al.* Evaluation of patients after treatment of arterial priapism with selective micro-embolization. *Scand J Urol Nephrol*, 2006. 40: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/16452056>
598. Cantasdemir, M., *et al.* Posttraumatic high-flow priapism in children treated with autologous blood clot embolization: long-term results and review of the literature. *Pediatr Radiol*, 2011. 41: 627.
<https://www.ncbi.nlm.nih.gov/pubmed/21127852>
599. Shapiro, R.H., *et al.* Post-traumatic priapism treated with selective cavernosal artery ligation. *Urology*, 1997. 49: 638.
<https://www.ncbi.nlm.nih.gov/pubmed/9111644>
600. Virag, R., *et al.* Preventive treatment of priapism in sickle cell disease with oral and self-administered intracavernous injection of etilefrine. *Urology*, 1996. 47: 777.
<https://www.ncbi.nlm.nih.gov/pubmed/8650886>
601. Fowler, J.E., Jr., *et al.* Priapism associated with the sickle cell hemoglobinopathies: prevalence, natural history and sequelae. *J Urol*, 1991. 145: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/1984102>
602. Mantadakis, E., *et al.* Prevalence of priapism in children and adolescents with sickle cell anemia. *J Pediatr Hematol Oncol*, 1999. 21: 518.
<https://www.ncbi.nlm.nih.gov/pubmed/10598664>
603. Morrison, B.F., *et al.* Stuttering priapism: insights into pathogenesis and management. *Curr Urol Rep*, 2012. 13: 268.
<https://www.ncbi.nlm.nih.gov/pubmed/22648304>
604. Roizenblatt, M., *et al.* Priapism is associated with sleep hypoxemia in sickle cell disease. *J Urol*, 2012. 188: 1245.
<https://www.ncbi.nlm.nih.gov/pubmed/22902014>
605. Mocniak, M., *et al.* The use of sudafed for priapism in pediatric patients with sickle cell disease. *J Pediatr Nurs*, 2012. 27: 82.
<https://www.ncbi.nlm.nih.gov/pubmed/22041221>
606. Gbadoe, A.D., *et al.* Management of sickle cell priapism with etilefrine. *Arch Dis Child*, 2001. 85: 52.
<https://www.ncbi.nlm.nih.gov/pubmed/11420201>
607. Okpala, I., *et al.* Etilefrine for the prevention of priapism in adult sickle cell disease. *Br J Haematol*, 2002. 118: 918.
<https://www.ncbi.nlm.nih.gov/pubmed/12181066>
608. Yuan, J., *et al.* Insights of priapism mechanism and rationale treatment for recurrent priapism. *Asian J Androl*, 2008. 10: 88.
<https://www.ncbi.nlm.nih.gov/pubmed/18087648>
609. Levine, L.A., *et al.* Gonadotropin-releasing hormone analogues in the treatment of sickle cell anemia-associated priapism. *J Urol*, 1993. 150: 475.
<https://www.ncbi.nlm.nih.gov/pubmed/8326584>
610. Rachid-Filho, D., *et al.* Treatment of recurrent priapism in sickle cell anemia with finasteride: a new approach. *Urology*, 2009. 74: 1054.
<https://www.ncbi.nlm.nih.gov/pubmed/19616292>

611. DeCastro, B.J., *et al.* Oral ketoconazole for prevention of postoperative penile erection: a placebo controlled, randomized, double-blind trial. *J Urol*, 2008. 179: 1930.
<https://www.ncbi.nlm.nih.gov/pubmed/18353393>
612. Gupta, S., *et al.* A possible mechanism for alteration of human erectile function by digoxin: inhibition of corpus cavernosum sodium/potassium adenosine triphosphatase activity. *J Urol*, 1998. 159: 1529.
<https://www.ncbi.nlm.nih.gov/pubmed/9554348>
613. Daoud, A.S., *et al.* The effect of Vigabatrin, Lamotrigine and Gabapentin on the fertility, weights, sex hormones and biochemical profiles of male rats. *Neuro Endocrinol Lett*, 2004. 25: 178.
<https://www.ncbi.nlm.nih.gov/pubmed/15349082>
614. Perimenis, P., *et al.* Gabapentin in the management of the recurrent, refractory, idiopathic priapism. *Int J Impot Res*, 2004. 16: 84.
<https://www.ncbi.nlm.nih.gov/pubmed/14963477>
615. D'Aleo, G., *et al.* Favorable response to intrathecal, but not oral, baclofen of priapism in a patient with spinal cord injury. *Spine (Phila Pa 1976)*, 2009. 34: E127.
<https://www.ncbi.nlm.nih.gov/pubmed/19179913>
616. Moreira, D.M., *et al.* Recurrent priapism in the young patient treated with baclofen. *J Pediatr Urol*, 2006. 2: 590.
<https://www.ncbi.nlm.nih.gov/pubmed/18947688>
617. Vaidyanathan, S., *et al.* Management of recurrent priapism in a cervical spinal cord injury patient with oral baclofen therapy. *Spinal Cord*, 2004. 42: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/14765150>
618. Kato, G.J. Priapism in sickle-cell disease: a hematologist's perspective. *J Sex Med*, 2012. 9: 70.
<https://www.ncbi.nlm.nih.gov/pubmed/21554552>
619. Meier, E.R., *et al.* Sickle cell disease in children. *Drugs*, 2012. 72: 895.
<https://www.ncbi.nlm.nih.gov/pubmed/22519940>
620. Saad, S.T., *et al.* Follow-up of sickle cell disease patients with priapism treated by hydroxyurea. *Am J Hematol*, 2004. 77: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/15307105>
621. Bivalacqua, T.J., *et al.* Establishment of a transgenic sickle-cell mouse model to study the pathophysiology of priapism. *J Sex Med*, 2009. 6: 2494.
<https://www.ncbi.nlm.nih.gov/pubmed/19523035>
622. Burnett, A.L., *et al.* Long-term oral phosphodiesterase 5 inhibitor therapy alleviates recurrent priapism. *Urology*, 2006. 67: 1043.
<https://www.ncbi.nlm.nih.gov/pubmed/16698365>
623. Burnett, A.L., *et al.* Feasibility of the use of phosphodiesterase type 5 inhibitors in a pharmacologic prevention program for recurrent priapism. *J Sex Med*, 2006. 3: 1077.
<https://www.ncbi.nlm.nih.gov/pubmed/17100941>
624. Champion, H.C., *et al.* Phosphodiesterase-5A dysregulation in penile erectile tissue is a mechanism of priapism. *Proc Natl Acad Sci U S A*, 2005. 102: 1661.
<https://www.ncbi.nlm.nih.gov/pubmed/15668387>
625. Pierorazio, P.M., *et al.* Daily phosphodiesterase type 5 inhibitor therapy as rescue for recurrent ischemic priapism after failed androgen ablation. *J Androl*, 2011. 32: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/21127306>
626. Rutchik, S., *et al.* Successful treatment of recalcitrant priapism using intercorporeal injection of tissue plasminogen activator. *J Urol*, 2001. 166: 628.
<https://www.ncbi.nlm.nih.gov/pubmed/11458096>

5. CONFLICT OF INTEREST

All members of the EAU Male Sexual Dysfunction Guidelines Panel have provided disclosure statements of all relationships which they have and which may be perceived as a potential source of conflict of interest. This information is publically accessible through the EAU website <https://uroweb.org/guideline/>. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.



EAU Guidelines on Male Infertility

A. Jungwirth (Chair), T. Diemer (Vice-chair), Z. Kopa,
C. Krausz, H. Tournaye
Guidelines Associates: B. Kelly, R. Pal

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1. INTRODUCTION

1.1 Aim

The European Association of Urology (EAU) Guidelines Panel on Male Infertility has prepared these Guidelines to assist urologists and healthcare professionals from related specialties in the treatment of male infertility. Urologists are usually the initial specialty responsible for assessing men when male infertility is suspected. However, infertility can be a multifactorial condition requiring multidisciplinary involvement.

It must be emphasised that clinical guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not and should not purport to be a legal standard of care.

1.2 Publication history

The EAU Male Infertility Guidelines were first published in 2001, followed by full-text updates in 2004, 2007, 2010, 2013, 2014 and 2015. In 2016 a scoping search was performed, covering all areas of the guideline and it was updated accordingly.

1.3 Available Publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Male Infertility Guidelines. These are abridged versions which may require consultation together with the full text versions. The Male Infertility Panel published a number of scientific publications in the EAU journal *European Urology* [1-3]. A separate scientific paper on Vasectomy was published in 2012 [2]. All texts can be viewed and downloaded for personal use at the society website: <http://www.uroweb.org/guidelines/male-infertility/>.

1.4 Panel composition

The Male Infertility Guidelines Panel consists of urologists, endocrinologists and gynaecologists with special training in andrology and experience in the diagnosis and treatment of male infertility. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guideline/male-infertility/>.

2. METHODS

2.1 Introduction

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence [4]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://www.uroweb.org/guideline/>.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address. In particular, the Male Infertility Guidelines have been endorsed by the Hellenic Society of Reproductive Medicine.

The recommendations provided in these guidelines are based on a systematic literature search performed by the panel members. The controlled vocabulary of the MeSH database was used alongside a free text protocol, combining “male infertility” with the terms “diagnosis”, “epidemiology”, “investigations”, “treatment”, “spermatogenic failure”, “genetic abnormalities”, “obstruction”, “hypogonadism”, “varicocele”, “cryptorchidism”, “testicular cancer”, “male accessory gland infection”, “idiopathic”, “contraception”, “ejaculatory dysfunction”, and “cryopreservation”.

For the 2017 print a scoping search was performed, covering all areas of the guideline, starting from the last cut-off date April 2015 with a cut-off date of April 2016. Embase, Medline and the Cochrane Central Register of Controlled Trials databases were searched, with a limitation to reviews, meta-analyses or meta-analysis of randomised controlled trials. A total of 409 unique records were identified, retrieved and screened for relevance, of which nine publications were selected for inclusion. A detailed search strategy is available online: <http://www.uroweb.org/guideline/male-infertility/>.

2.2 Review

This document was subject to peer review prior to publication in 2015.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2018 update of the Male Infertility Guidelines. Ongoing systematic reviews include:

- What are the benefits of nutritional and/or medical therapy on the pregnancy rate and semen parameters and harms in males with idiopathic infertility? [5].

3. EPIDEMIOLOGY AND AETIOLOGY – GENERAL PRINCIPLES

3.1 Introduction

Definition

“Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year”, World Health Organization (WHO) [6].

About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child. Three percent of women remain involuntarily childless, while 6% of parous women are not able to have as many children as they would wish [7]. Infertility affects both men and women. In 50% of voluntarily childless couples, a male-infertility-associated factor is found together with with abnormal semen parameters. A fertile partner may compensate for the fertility problem of the man and thus infertility usually manifests if both partners have reduced fertility [6]. Male fertility can be reduced as a result of [6]:

- congenital or acquired urogenital abnormalities;
- malignancies;
- urogenital tract infections;
- increased scrotal temperature (e.g. as a consequence of varicocele);
- endocrine disturbances;
- genetic abnormalities;
- immunological factors.

In 30-40% of cases, no male-infertility-associated factor is found (idiopathic male infertility). These men present with no previous history of diseases affecting fertility and have normal findings on physical examination and endocrine, genetic and biochemical laboratory testing. However, semen analysis might reveal pathological findings in the spermogram (see 4.2.1). Table 1 summarises the main male-infertility-associated factors. Idiopathic male infertility is assumed to be caused by several factors, including endocrine disruption as a result of environmental pollution, reactive oxygen species, or genetic and epigenetic abnormalities.

Table 1: Male infertility causes and associated factors and percentage of distribution in 10,469 patients [8]

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
<i>All</i>	100%	11.2%
<i>Infertility of known (possible) cause</i>	42.6%	42.6%
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm autoantibodies	3.9	-
Testicular tumour	1.2	2.8
Others	5.0	1.2
<i>Idiopathic infertility</i>	30.0	13.3
<i>Hypogonadism</i>	10.1	16.4
Klinefelter's syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	< 0.1	0.3
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
Others	0.8	0.8
<i>General/systemic disease</i>	2.2	0.5
<i>Cryopreservation due to malignant disease</i>	7.8	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6
Leukaemia	0.7	2.2
Sarcoma	0.6	0.9
<i>Disturbance of erection/ejaculation</i>	2.4	-
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (CBAVD)	0.5	3.
Others	0.8	1.9

CBAVD = Congenital Bilateral Absence of the Vas Deferens

3.2 Recommendations on epidemiology and aetiology

Recommendations	GR
Investigate both partners simultaneously, to categorise infertility.	C
Include the fertility status of the female partner in the diagnosis and management of male subfertility because this might determine the final outcome.	B
Examine all men diagnosed with fertility problems, including men with abnormal semen parameters for urogenital abnormalities.	C

4. PROGNOSTIC FACTORS AND DIAGNOSTIC EVALUATION - GENERAL PRINCIPLES

4.1 Prognostic factors

Prognostic factors for male infertility are:

- duration of infertility;
- primary or secondary infertility;
- results of semen analysis;
- age and fertility status of female partner.

The cumulative pregnancy rate is 27% in infertile couples with two years of follow-up and oligozoospermia as the primary cause of infertility [9]. Female age is the most important single variable influencing outcome in assisted reproduction [10]. Compared to a woman aged 25 years, the fertility potential of a woman aged 35 years is reduced to 50%, to 25% at 38 years, and less than 5% at over 40 years. In many Western countries, women postpone their first pregnancy until after their education and starting a career.

4.2 Diagnostic evaluation

4.2.1 Semen analysis

A medical history and physical examination are standard assessments in all men, including scrotal ultrasound (US) [11] and semen analysis. A comprehensive andrological examination is indicated if semen analysis shows abnormalities compared with reference values (Table 2). Important treatment decisions are based on the results of semen analysis, therefore, it is essential that the complete laboratory work-up is standardised. Ejaculate analysis has been standardised by the WHO and disseminated by publication of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) [12]. It is the consensus that modern spermatology must follow these guidelines.

Table 2: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10 ⁶ /ejaculate)	39 (33-46)
Sperm concentration (10 ⁶ /mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10 ⁶ /mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (μmol/ejaculate)	> 2.4
Seminal fructose (μmol/ejaculate)	> 13
Seminal neutral glucosidase (mU/ejaculate)	< 20

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

4.2.1.1 Frequency of semen analysis

If the results of semen analysis are normal according to WHO criteria, one test is sufficient. If the results are abnormal in at least two tests, further andrological investigation is indicated. It is important to differentiate between the following:

- oligozoospermia: < 15 million spermatozoa/mL;
- asthenozoospermia: < 32% progressive motile spermatozoa;
- teratozoospermia: < 4% normal forms.

Often, all three anomalies occur simultaneously, which is defined as oligo-astheno-teratozoospermia (OAT) syndrome. As in azoospermia, in extreme cases of oligozoospermia (spermatozoa < 1 million/mL), there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

4.2.2 **Recommendations for the diagnostic evaluation of male infertility**

Recommendations	GR
Perform semen analyses according to the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn).	A*
Perform further andrological assessment when semen analysis is abnormal in at least two tests.	A*
Adhere to the 2010 WHO Manual for the standardised investigation, diagnosis and management of the infertile male for diagnosis and evaluation of male subfertility.	C

*Upgraded following panel consensus.

5. CONDITIONS CAUSING MALE INFERTILITY

5.1 Primary Spermatogenic Failure

5.1.1 **Aetiology**

The causes of testicular deficiency are summarised in Table 3.

Table 3: Causes of testicular deficiency

Factors	Causes
Congenital	Anorchia
	Testicular dysgenesis/cryptorchidism
	Genetic abnormalities (karyotype, Y-chromosome deletions)
Acquired	Trauma
	Testicular torsion
	Post-inflammatory forms, particularly mumps orchitis
	Exogenous factors (medications, cytotoxic or anabolic drugs, irradiation, heat)
	Systemic diseases (liver cirrhosis, renal failure)
	Testicular tumour
	Varicocele
Surgery that may compromise vascularisation of the testes and lead to testicular atrophy	
Idiopathic	Unknown aetiology
	Unknown pathogenesis

5.1.2 **Diagnostic evaluation**

Routine investigations include semen analysis and hormonal determinations. Other investigations may be required depending on the individual situation.

Typical findings from the history and physical examination of a patient with testicular deficiency are:

- cryptorchidism (uni- or bilateral);
- testicular torsion and trauma;
- genitourinary infection;
- exposure to environmental toxins;
- gonadotoxic medication (anabolic drugs, SSRIs, etc);
- exposure to radiation or cytotoxic agents;
- testicular cancer;
- absence of testes;
- abnormal secondary sexual characteristics;
- gynaecomastia;
- abnormal testicular volume and/or consistency; and
- varicocele.

5.1.2.1 Semen analysis

In non-obstructive azoospermia (NOA), semen analysis shows normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3000 g for fifteen minutes and a thorough microscopic examination by phase contrast optics at $\times 200$ magnification of the pellet. All samples can be stained and re-examined microscopically [12].

5.1.2.2 Hormonal determinations

In men with testicular deficiency, Hypergonadotropic hypogonadism is usually present, with high levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH), and sometimes low levels of testosterone. Generally, the levels of FSH correlate with the number of spermatogonia: when spermatogonia are absent or markedly diminished, FSH values are usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH values are within the normal range. However, for an individual patient, FSH levels do not accurately predict the spermatogenesis status because men with maturation arrest histology could have normal FSH and testis volume and still be azoospermic [13, 14].

5.1.2.3 Ultrasonography

In addition to physical examination, a scrotal US may be helpful in finding signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) and may demonstrate signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and testis tumours. For patients with a low seminal volume and in whom distal obstruction is suspected, transrectal ultrasound (TRUS) is essential [11].

5.1.2.4 Testicular biopsy

Testicular biopsy can be part of intracytoplasmic sperm injection (ICSI) treatment in patients with clinical evidence of NOA. Testicular sperm extraction (TESE) is the technique of choice. Spermatogenesis may be focal, which means that in about 50% of men with NOA, spermatozoa can be found and used for ICSI. There is a good correlation between the histology found upon diagnostic biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI [15-17]. However, no threshold value has been found for FSH, inhibin B, or testicular volume and successful sperm harvesting. When there are complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is virtually zero and therefore TESE procedures are contraindicated. Microsurgical TESE yields the highest sperm retrieval rates, and multiple TESE is superior to conventional TESE. Microsurgical TESE should be preferred in severe cases of non-obstructive azoospermia [18-22].

The results of ICSI are worse when using sperm retrieved from men with NOA compared to sperm from ejaculated semen and from men with obstructive azoospermia (OA) [23-27]. Birth rates are lower in NOA vs. OA (19% vs 28%) [28, 29]. ICSI results in significantly lower fertilisation and implantation rates. In longitudinal studies including patients with NOA as defined by testicular histopathology, only one out of seven NOA patients embarking for TESE and eventually ICSI will father their genetically-own child [30]. Neonatal health in terms of birth parameters, major anomalies and chromosomal aberrations in a large cohort of children born after use of non-ejaculated sperm are comparable to the outcome of children born after use of ejaculated sperm [31].

5.1.3 Summary of evidence and recommendations

Summary of evidence	LE
The WHO laboratory manual proposes reference values based on fertility therefore these reference values do not allow classification of men as infertile.	2a
Impaired spermatogenesis is often associated with elevated FSH concentration.	3
For patients with NOA who have spermatozoa in their testicular biopsy, intracytoplasmic sperm injection (ICSI) with fresh or cryopreserved spermatozoa is the only therapeutic option. Spermatozoa are found by a TESE procedure in about 50% of patients with NOA.	2a
Pregnancies and live births are eventually obtained in 30-50% of couples with NOA, when spermatozoa have been found in the testicular biopsy.	3

Recommendations	GR
For men who are candidates for sperm retrieval, give appropriate genetic counselling even when testing for genetic abnormalities was negative.	A
In men with non-obstructive azoospermia (NOA), perform simultaneous testicular biopsy with multiple testicular sperm extraction (TESE) (or micro- TESE) to define spermatogenesis and diagnose intratubular germ cell neoplasia of unclassified type (ITGCNU) and eventually cryopreservation of sperm.	A

5.2 Genetic disorders in infertility

All urologists working in andrology must have an understanding of genetic abnormalities associated with infertility, so that they can provide correct advice to couples seeking fertility treatment. Men with very low sperm counts can be offered a reasonable chance of paternity, using in vitro fertilisation (IVF), ICSI and sperm harvesting from the testes in case of azoospermia. However, the spermatozoa of infertile men show an increased rate of aneuploidy, structural chromosomal abnormalities, and DNA damage, carrying the risk of passing genetic abnormalities to the next generation. Current routine clinical practice is based on the screening of genomic DNA from peripheral blood samples, however, screening of chromosomal anomalies in spermatozoa is also feasible and can be performed in selected cases [32].

5.2.1 Chromosomal abnormalities

Chromosome abnormalities can be numerical (e.g. trisomy) or structural (e.g. inversions or translocations). In a survey of pooled data from eleven publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% [33]. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities was 0.38% in pooled data from three series, with a total of 94,465 newborn male infants, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) autosomal abnormalities [33]. The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with a spermatozoa count < 5 million/mL already show a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities compared with the general population [34, 35]. Men with NOA are at highest risk, especially for sex chromosomal anomalies.

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is indicated in men with azoospermia or oligozoospermia (spermatozoa < 10 million/mL) [35]. A recent study proposes to restrict karyotype to NOA men with the purpose to prevent adverse pregnancy outcomes [36]. If there is a family history of recurrent spontaneous abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

5.2.1.1 Sex chromosome abnormalities (Klinefelter's syndrome and variants [47,XXY; 46,XY/47,XXY mosaicism])

Klinefelter's syndrome is the most common sex chromosome abnormality [37]. Adult men with Klinefelter's syndrome have small firm testicles, devoid of germ cells. The phenotype varies from a normally virilised man to one with the stigmata of androgen deficiency, including female hair distribution, scant body hair, and long arms and legs due to late epiphyseal closure. Leydig cell function is commonly impaired in men with Klinefelter's syndrome [38]. Testosterone levels may be normal or low, oestradiol levels normal or elevated, and FSH levels increased. Libido is often normal despite low testosterone levels, but androgen replacement may be needed as the patient ages.

Germ cell presence and sperm production are variable in men with Klinefelter's mosaicism, 46,XY/47,XXY. Based on sperm fluorescence *in situ* hybridisation (FISH) studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidy (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI [39].

The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism [40, 41] and in 1.36-25% of men with somatic karyotype 47,XXY [42-45]. In patients with azoospermia, TESE (42%) or micro-TESE (57%) can be proposed as a therapeutic option since spermatozoa can be recovered in about 50% of cases [46]. There is growing evidence that TESE or micro TESE yields higher sperm recovery rates when done at younger age. Numerous healthy children have been born using ICSI without pre-implantation genetic diagnosis (PGD) and the conception of one 47,XXY foetus has been reported [37]. However, a study of ICSI combined with PGD in 113 embryos reported a significant fall in the rate of normal embryos for couples with Klinefelter's syndrome with respect to controls (54% vs. 77.2%) [45]. Due to the significant increase of sex chromosomal and autosomal abnormalities in the embryos of Klinefelter's patients, PGD or amniocentesis analysis should be considered.

Follow-up (possibly every year) of men with Klinefelter's syndrome is required and androgen replacement therapy should be started after fertility issues have been addressed and when testosterone level is in the range of hypoandrogenism.

TESE in peripubertal or pre-pubertal Klinefelter boys aiming at cryopreservation of testicular spermatogonial stem cells is to be considered experimental and should only be performed within a research protocol [47].

5.2.1.2 *Autosomal abnormalities*

Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner has an autosomal karyotype abnormality. The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions, and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the foetus. As with Klinefelter's syndrome, sperm FISH analysis provides a more accurate risk estimation of affected offspring, however, the diffusion of this genetic test is largely limited by the availability of laboratories able to perform this analysis. When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed [48, 49].

5.2.1.3 *Sperm chromosomal abnormalities*

Sperm can be examined for their chromosomal constitution using multicolour FISH both in men with normal karyotype and with anomalies. Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis [33, 50-52] and with translocations [53]. Florescence *in situ* hybridisation analysis of spermatozoa is only indicated for specific andrology conditions e.g. macrocephalia [52].

5.2.2 **Genetic defects**

5.2.2.1 *X-linked genetic disorders and male fertility*

Each man has only one X-chromosome. An X-linked recessive disorder manifests in males. The defect will be transmitted to daughters, but not to sons.

5.2.2.2 *Kallmann syndrome*

Patients with Kallmann syndrome have hypogonadotropic hypogonadism and anosmia, but may also have other clinical features, including facial asymmetry, cleft palate, colour blindness, deafness, maldescended testes, and unilateral renal aplasia. This syndrome can be due to mutation in the Kalig-1 gene [on the X-chromosome] or in several other autosomal genes and should be tested [52, 53].

Spermatogenesis can be relatively easily induced by hormonal treatment [54], therefore, genetic screening prior to therapy is advisable although it is limited by the rarity of specialised genetic laboratories that can offer this genetic test. Treatment with gonadotropins allows natural conception in most cases, even for men with a relatively low sperm count. Thus, identification of the involved gene (X-linked, autosomal dominant or recessive) can help to provide more accurate genetic counselling, that is, risk estimation for transmission to the offspring.

5.2.2.3 *Mild androgen insensitivity syndrome*

The Androgen Receptor (AR) gene is located on the long arm of the X-chromosome. Mutations in the AR gene may result in mild to complete androgen insensitivity. The phenotypic features of complete androgen insensitivity syndrome are female external genitalia and absence of pubic hair (Morris syndrome). In partial androgen insensitivity syndrome, phenotypes range from predominantly female phenotype through ambiguous genitalia, to predominantly male phenotype with micropenis, perineal hypospadias, and cryptorchidism. The latter phenotype is also termed Reifenstein syndrome. In the forementioned severe forms of androgen resistance, there is no risk of transmission because affected men cannot generate their own biological children using the current technologies. Patients with mild androgen insensitivity syndrome have male infertility as their primary or even sole symptom. Disorders of the androgen receptor causing infertility in the absence of any genital abnormality are rare, and only a few mutations have been reported in infertile [55-58] or fertile [59] men.

5.2.2.4 *Other X-disorders*

An unexpectedly high number of genes with a testis-specific or enriched expression pattern have been identified on the X-chromosome, and in particular, premeiotic genes are over-represented on the X-chromosome compared with autosomal chromosomes [60]. Nevertheless, to date only a few genes have been screened in relatively small populations and none of them appear relevant for male infertility [61, 62]. On the other hand, two recent independent studies showed a significantly higher deletion load on the X-chromosome in men with spermatogenic failure with respect to normozoospermic controls [63, 64].

5.2.3 **Y-chromosome and male infertility**

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc [65]. Clinically relevant deletions remove partially, or in most cases completely, one or more of the AZF regions, and are the most frequent molecular genetic cause of severe oligozoospermia and azoospermia [66]. In each AZF region, there are several spermatogenesis candidate genes [67]. Deletions occur en bloc (i.e. removing more than one gene), thus, it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and it is unclear if they all participate in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region and concern the USP9Y gene. These studies have suggested that USP9Y is most likely to be a “fine tuner” of sperm production, and its specific screening is not advised [68].

5.2.3.1 *Clinical implications of Y microdeletions*

The clinical significance of Yq microdeletions can be summarised as follows:

- They are not found in normozoospermic men, proving there is a clear cut cause-and-effect relationship between Y-deletions and spermatogenic failure [69].
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men.
- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%).
- AZFc deletions are most common (65-70%), followed by Y-deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are rare (5%).
- Complete removal of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome), while complete removal of the AZFb region is associated with spermatogenic rest. Complete removal of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Classical (complete) AZF deletions do not confer a risk for cryptorchidism or testicular cancer [66].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [66].

5.2.3.1.1 Testing for Y microdeletions

Indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count < 5 million/mL). Thanks to the European Academy of Andrology (EAA) guidelines [66] and the EAA/EMQN (European Molecular Genetics Quality Network) external quality control programme (<http://www.emqn.org/emqn/>), Yq testing has become more reliable in different routine genetic laboratories. The EAA guidelines provide a set of primers capable of detecting > 95% of clinically relevant deletions [70].

5.2.3.1.2 Genetic counselling for AZF deletions

After conception, any Y-deletions are transmitted obligatorily to the male offspring, and genetic counselling is therefore mandatory. In most cases, father and son have the same microdeletion [70], but occasionally the son has a larger one [71]. The extent of spermatogenic failure (still in the range of azoo-/oligozoospermia) cannot be predicted entirely in the son, due to the different genetic background and the presence or absence of environmental factors with potential toxicity for reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosomes [72, 73], indicating a potential risk for any offspring to develop 45,X0 Turner's syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia [74]. Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal [66, 70]. This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortion of embryos bearing a 45,X0 karyotype. When ICSI is used in the presence of a Y microdeletion, long-term follow-up of any male children is needed with respect to their fertility status, and cryopreservation of spermatozoa at a young age can be considered.

5.2.3.1.3 Y-chromosome: 'gr/gr' deletion

A new type of Yq deletion, known as the gr/gr deletion, has been described in the AZFc region [75]. This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. This type of deletion confers a 2.5-8 fold increased risk for oligozoospermia [70, 76-78]. The frequency of gr/gr deletion in oligozoospermic patients is ~4%.

According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production [77, 78]. It is worth noting that both the frequency of gr/gr deletion and its phenotypic expression vary between different ethnic groups, depending on the Y-chromosome background. For example, in some Y haplogroups, the deletion is fixed and appears to have no negative effect on spermatogenesis. Consequently, the routine screening for gr/gr deletion is still a debated issue, especially in those laboratories serving diverse ethnic

and geographic populations. A large multicentre study has shown that gr/gr deletion is a potential risk factor for testicular germ cell tumours [79]. However, these data need further confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noting that partial AZFc deletions, gr/gr and b2/b3, may predispose to complete AZFc deletion in the next generation [80, 81].

5.2.3.1.4 Autosomal defects with severe phenotypic abnormalities and infertility

Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility. Among them, Prader-Willy Syndrome, Bardet-Biedl Syndrome, Noonan's Syndrome, Myotonic dystrophy, dominant polycystic kidney disease, 5 α -reductase deficiency, etc. Patients with these defects will be well known to doctors, often from childhood. A fertility problem must be managed in the context of the care of the man as a whole including the couple's ability to care for a child.

5.2.4 **Cystic fibrosis mutations and male infertility**

Cystic fibrosis (CF) is a fatal autosomal-recessive disorder. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p. It encodes a membrane protein that functions as an ion channel and influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis.

Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR gene mutations and was found in ~2% of men with OA attending a clinic in Edinburgh, UK [82]. The incidence in men with OA varies between different countries. The clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be very carefully examined to exclude CBAVD, particularly those with a semen volume < 1.5 mL and pH < 7.0. Approximately 1,500 mutations are listed on the CFTR database <http://www.genetsickkids.on.ca/cftr/>. The most frequently found mutations are the F508, R117H and W1282X, but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [83, 84]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [79], it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CBAVD patient. As more mutations are defined and tested for, almost all men with CBAVD will probably be found to have mutations. It is not practical to test for all known mutations, because many have a very low prevalence in a particular population. Routine testing is usually restricted to the most common mutations in a particular community through the analysis of a mutation panel. Given that this is a recessive disease if a second mutation is not found with the routine panel, a second step analysis is advised which comprises the direct sequencing of the entire gene. Men with CBAVD often have mild clinical stigmata of CF (e.g., history of chest infections). When a man has CBAVD, it is important to test also his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider very carefully whether to proceed with ICSI using the male's sperm, as the risk of having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is ~0.4% [85].

5.2.4.1 *Unilateral or bilateral absence/abnormality of the vas and renal anomalies*

Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [86]. Consequently, in these subjects CFTR mutation screening is not indicated. Men with unilateral absence of the vas deferens are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. CFTR gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. An abdominal ultrasound should be undertaken both in unilateral and bilateral absence of vas deferens. Findings may range from unilateral absence of the vas deferens with ipsilateral absence of the kidney, to bilateral vessel and renal abnormalities, such as pelvic kidney [87].

5.2.4.2 *Unknown genetic disorders*

Considering the predicted high number of genes involved in male gametogenesis, it is likely that most idiopathic forms of spermatogenic disturbances are caused by mutations or polymorphisms in spermatogenesis candidate genes [61]. However, despite an intensive search for new genetic factors, no clinically relevant gene mutations or polymorphisms (except those related to the Y-chromosome) have so far been identified [61, 85, 88]. The introduction of new analytical approaches has provided evidence for the importance of Copy Number Variations (CNVs) [63, 64] and further advances are expected with Next Generation Sequencing. Intracytoplasmic sperm injection is used to enable men with severely damaged spermatogenesis to father children in situations formerly considered hopeless and where very few spermatozoa can be obtained. This has led to concern that children may be born with a foetal abnormality, because ICSI may enable defective sperm to bypass the selective processes of the female genital tract and egg covering.

Intracytoplasmic sperm injection babies have a higher risk of de novo sex chromosomal aberrations (about a threefold increase compared with natural conceptions) and paternally inherited structural abnormalities. Treatment with assisted reproductive technology was associated with increased risk of cardiovascular, musculoskeletal, urogenital, and gastrointestinal defects and cerebral palsy [89-91].

5.2.4.3 DNA fragmentation in spermatozoa

There is increased DNA damage in spermatozoa from men with oligozoospermia. This increase is associated with reduced chances of natural conception and an increased chance of early pregnancy loss [92].

5.2.4.4 Genetic counselling and ICSI

Initially, the couple should be given full information about the risks to the child in order to help them decide whether to proceed with ICSI. Where there is conflict between the wishes of the couple and the interests of the future child, it may be ethically correct to withhold therapy. When both partners are known to carry defects (e.g., CFTR mutations), there is up to a 50% chance of the child developing a clinical condition. Many clinicians and infertility clinic personnel may consider it unethical to proceed because their duty of care to the future child and the interests of society outweigh the wishes of the individual couple. If there is a conflict that cannot be resolved by agreement, the interests of a future child probably take precedence over the interests of a couple. The couple also needs to give consideration to pre-implantation diagnosis.

5.2.5 Summary of evidence and recommendations for genetic disorders in male infertility

Summary of evidence	LE
In men with spermatogenic damage there is a higher prevalence of chromosome abnormalities, reaching the highest frequency in NOA men.	1b
AZF deletions are clear-cut causes of spermatogenic impairments with diagnostic and prognostic value for TESE.	1a
AZF deletions will be transmitted to the son.	1a
gr/gr deletion has been confirmed as a significant risk factor for impaired sperm production, whereas further evidence of the prognostic significance of gr/gr and development of a testicular germ cell tumour is needed.	2b

Recommendations	GR
Obtain standard karyotype analysis in all men with damaged spermatogenesis (spermatozoa < 10 million/mL) who are seeking fertility treatment by in vitro fertilisation (IVF).	B
Provide genetic counselling in all couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	A
For all men with Klinefelter's syndrome, provide long-term endocrine follow-up and androgen replacement therapy, if necessary.	A
Do not test for microdeletions in men with obstructive azoospermia (OA) when intracytoplasmic sperm injection (ICSI) is used because spermatogenesis should be normal.	A
Inform men with Yq microdeletion and their partners who wish to proceed with intracytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to daughters.	A
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence), test the man and his partner for cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations.	A

5.3 Obstructive azoospermia

Obstructive azoospermia (OA) is the absence of spermatozoa and spermatogenic cells in semen and post-ejaculate urine due to obstruction. OA is less common than NOA and occurs in 15-20% of men with azoospermia. Men with OA present with normal FSH, normal size testes, and epididymal enlargement. Sometimes, the vas deferens is absent (CBAVD or Congenital Unilateral Absence of the Vas Deferens (CUAVD)). Obstruction in primary infertile men is frequently present at the epididymal level.

5.3.1 Classification

5.3.1.1 Intratesticular obstruction

Intratesticular obstruction occurs in 15% of men with OA [93]. Congenital forms are less common than acquired forms (post-inflammatory or post-traumatic).

5.3.1.2 Epididymal obstruction

Epididymal obstruction is the most common cause of OA, affecting 30-67% of azoospermic men [93-97]. Congenital epididymal obstruction usually manifests as CBAVD, which is associated with at least one mutation of the CF gene in 82% of cases [96]. Congenital forms of epididymal obstruction include chronic sinopulmonary infections (Young's syndrome) [98]. Acquired forms secondary to acute (e.g., gonococcal) and subclinical (e.g., chlamydial) epididymitis are most common [99, 100]. Other causes may be trauma or surgical intervention [101, 102].

5.3.1.3 Vas deferens obstruction

Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy [99]. Approximately 2-6% of these men request vasectomy reversal (see Chapter 5.6). Vasal obstruction may also occur after hernia repair [103, 104]. The most common congenital vasal obstruction is CBAVD, often accompanied by CF. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively [105] (see Chapter 5.2).

5.3.1.4 Ejaculatory duct obstruction

Ejaculatory duct obstruction is found in 1-3% of cases of OA [93] and is classified as either cystic or post-inflammatory. Cystic obstructions are usually congenital (i.e., Mullerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are typically midline. In urogenital sinus abnormalities, one or both ejaculatory ducts empty into the cyst [106], while in Mullerian duct anomalies, the ejaculatory ducts are laterally displaced and compressed by the cyst [107]. Paramedian or lateral intraprostatic cysts are rare [108]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to urethroprostatitis [109]. Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low semen volume, decreased or absent seminal fructose, and acid pH. The seminal vesicles are usually dilated (anterior-posterior diameter > 15 mm) [109, 110].

5.3.1.5 Functional obstruction of the distal seminal ducts

Functional obstruction of the distal seminal ducts might be attributed to local neuropathy [111]. This abnormality is often associated with urodynamic dysfunction. Impaired sperm transport may be idiopathic or associated with selective serotonin reuptake inhibitor (SSRI) medication as well.

5.3.2 Diagnostic evaluation

5.3.2.1 Clinical history

Clinical history taking should follow the suggestions for the diagnostic evaluation of infertile men (See Chapter 4.2).

5.3.2.2 Clinical examination

Clinical examination should follow suggestions for the diagnostic evaluation of infertile men. OA is indicated by at least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with:

- OA and concomitant partial testicular failure;
- enlarged and hardened epididymis;
- nodules in the epididymis or vas deferens;
- absence or partial atresia of the vas.

5.3.2.3 Semen analysis

At least two examinations must be carried out at an interval of two to three months, according to the WHO (see Chapter 4.2). Azoospermia means the inability to detect spermatozoa after centrifugation at $\times 400$ magnification. When semen volume is low, a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in semen smears suggest complete seminal duct obstruction.

5.3.2.4 Hormone levels

Serum FSH levels should be normal, but do not exclude a testicular cause of azoospermia. FSH level is normal in 40% of men with primary spermatogenic failure. Inhibin B seems to have a higher predictive value for normal spermatogenesis [97].

5.3.2.5 Testicular biopsy

In selected cases, testicular biopsy is indicated to exclude spermatogenic failure. Testicular biopsy should be combined with extraction of testicular spermatozoa (i.e., TESE) for cryopreservation.

5.3.3 **Disease management**

5.3.3.1 *Intratesticular obstruction*

Only TESE allows sperm retrieval in these patients and is therefore recommended.

5.3.3.2 *Epididymal obstruction*

Microsurgical epididymal sperm aspiration (MESA) [112] is indicated in men with CBAVD. TESE and PESA (limited cryopreservation) are also viable options [113]. Usually, one MESA procedure provides sufficient material for several ICSI cycles [114] and it produces high pregnancy and fertilisation rates [115]. In patients with azoospermia due to acquired epididymal obstruction, microsurgical reconstruction is recommended, with the preferred technique being microsurgical intussusception tubulovasostomy [116]. Anatomical recanalisation following surgery may require three to eighteen months. Before microsurgery, and in all cases where recanalisation is impossible, epididymal spermatozoa should be aspirated and cryopreserved for use in ICSI [114]. Patency rates range between 60% and 87% [102, 117] and cumulative pregnancy rates between 10% and 43%. Recanalisation success rates may be adversely affected by pre-operative and intra-operative findings.

5.3.3.3 *Proximal vas deferens obstruction*

Proximal vas deferens obstruction after vasectomy requires microsurgical vasectomy reversal. Vasovasostomy is also required in rare cases of proximal vasal obstructions. The absence of spermatozoa in the intra-operative vas deferens fluid suggests the presence of a secondary epididymal obstruction, especially if the seminal fluid of the proximal vas has a thick “toothpaste” appearance. Microsurgical tubulovasostomy is then indicated.

5.3.3.4 *Distal vas deferens obstruction*

It is usually impossible to correct large bilateral vas deferens defects, resulting from involuntary excision of the vasa deferentia during hernia surgery in early childhood or previous orchidopexy [118]. In these cases TESE/MESA or proximal vas deferens sperm aspiration [119] can be used for cryopreservation for future ICSI.

5.3.3.5 *Ejaculatory duct obstruction*

The treatment of ejaculatory duct obstruction depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) [109] can be used in large post-inflammatory obstruction and when one or both ejaculatory ducts empty into an intraprostatic midline cyst. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision or unroofing of the cyst is required [109]. Intra-operative transrectal US (TRUS) makes this procedure safer. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the vas deferens can help to document opening of the ducts. The limited success rate of surgical treatment of ejaculatory duct obstruction in terms of spontaneous pregnancies should be weighed against sperm aspiration and ICSI. Complications following TURED include retrograde ejaculation due to bladder neck injury and urine reflux into the ejaculatory ducts, seminal vesicles, and vasa. The alternatives to TURED are MESA, TESE, proximal vas deferens sperm aspiration, seminal vesicle ultrasonically guided aspiration, and direct cyst aspiration. Spermatozoa can then be retrieved by antegrade seminal tract washout [120].

5.3.4 **Summary of evidence and recommendations for obstructive azoospermia**

Summary of evidence	LE
Obstructive lesions of the seminal tract are frequent in azoospermic or severely oligozoospermic patients with normal-sized testes and normal reproductive hormones.	3

Recommendations	GR
Perform microsurgical vasovasostomy or tubulovasostomy for azoospermia caused by vasal or epididymal obstruction.	B
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and percutaneous epididymal sperm aspiration (PESA) only when cryostorage of the material obtained is available.	B

5.4 Varicocele

Varicocele is a common abnormality which may be associated with the following andrological conditions:

- Failure of ipsilateral testicular growth and development,
- Symptoms of pain and discomfort,
- Male subfertility,
- Hypogonadism.

5.4.1 Classification

The following classification of varicocele [121] is useful in clinical practice:

- Subclinical: not palpable or visible at rest or during Valsava manoeuvre, but can be shown by special tests (Doppler ultrasound studies),
- Grade 1: palpable during Valsava manoeuvre, but not otherwise,
- Grade 2: palpable at rest, but not visible,
- Grade 3: visible and palpable at rest.

5.4.2 Diagnostic evaluation

The diagnosis of varicocele is made by clinical examination and should be confirmed by US investigation and colour Duplex analysis [121]. In centres where treatment is carried out by antegrade or retrograde sclerotherapy or embolisation, diagnosis is additionally confirmed by X-ray.

5.4.3 Basic considerations

5.4.3.1 Varicocele and fertility

Varicocele is a physical abnormality present in 11.7% of adult men and in 25.4% of men with abnormal semen analysis [122]. The exact association between reduced male fertility and varicocele is unknown, but a recent meta-analysis showed that semen improvement is usually observed after surgical correction [123]. Varicocelectomy can reverse sperm DNA damage [124].

5.4.3.2 Varicocelectomy

Varicocele repair has been a subject of debate for several decades. A meta-analysis of randomised controlled trials (RCTs) and observational studies in men with only clinical varicoceles showed that surgical varicocelectomy significantly improves semen parameters in men with abnormal semen parameters including men with non-obstructive azoospermia [123, 125, 126].

In randomised controlled studies, varicocele repair in men with a subclinical varicocele was found to be ineffective in increasing the chance of spontaneous pregnancies [127]. Also, in randomised studies that included mainly men with normal semen parameters no benefit was found in favour of treatment over observation [128]. A Cochrane review from 2013 concluded that there is evidence to suggest that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of pregnancy [129]. In a subgroup analyses of five RCTs comparing treatment to observation in men with a clinical varicocele, oligospermia and otherwise unexplained infertility, the analyses favoured treatment, with a combined odds ratio (OR) of 2.39 (95% CI 1.56 to 3.66) [129].

5.4.3.3 Prophylactic Varicocelectomy

In adolescents with a varicocele there is a significant risk of over-treatment since most adolescents with a varicocele will have no problem achieving pregnancy later in life [130]. Prophylactic treatment is only advised in case of documented growth deterioration of the testis as documented by serial clinical examinations and impaired semen quality.

5.4.4 Disease management

Several treatments are available for varicocele (Table 4). Current evidence indicates that microsurgical varicocelectomy is the most effective method among the different varicocelectomy techniques [130]. Microsurgical repair results in fewer complications and lower recurrence rates compared to the other techniques. This procedure, however, requires microsurgical training. The various other techniques are still considered viable options, although recurrences and hydrocele formation are more likely to occur.

Table 4: Recurrence and complication rates associated with treatments for varicocele

Treatment	Ref.	Recurrence/ Persistence %	Complication rates
Antegrade sclerotherapy	[131]	9	Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema.
Retrograde sclerotherapy	[132]	9.8	Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation.
Retrograde embolisation	[133, 134]	3.8-10	Pain due to thrombophlebitis, bleeding haematoma, infection, venous perforation, hydrocele, radiological complication (e.g., reaction to contrast media), misplacement or migration of coils, retroperitoneal haemorrhage, fibrosis, ureteric obstruction.
<i>Open operation</i>			
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele.
Inguinal approach	[135]	13.3	Possibility of missing out a branch of testicular vein.
High ligation	[136]	29	5-10% incidence of hydrocele (< 1%).
Microsurgical inguinal or subinguinal	[137, 138]	0.8-4	Post-operative hydrocele arterial injury, scrotal haematoma.
Laparoscopy	[139, 140]	3-7	Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis; bleeding; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum); pneumoscrotum; wound infection.

5.4.5 Summary of evidence and recommendations for varicocele

Summary of evidence	LE
The presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment: the majority of boys with a varicocele will have no fertility problems later in life.	3
Varicocele repair was shown to be effective in men with oligospermia, a clinical varicocele and otherwise unexplained infertility.	1a

Recommendations	GR
Treat varicoceles in adolescents with progressive failure of testicular development documented by serial clinical examination.	B
Do not treat varicoceles in infertile men who have normal semen analysis and in men with a subclinical varicocele.	A
Treat varicoceles in men with a clinical varicocele, oligospermia and otherwise unexplained infertility in the couple.	A

5.5 Hypogonadism

Hypogonadism is characterised by impaired testicular function, which may affect spermatogenesis and/or testosterone synthesis. The symptoms of hypogonadism depend on the degree of androgen deficiency and if the condition develops before or after pubertal development of the secondary sex characteristics.

5.5.1 Epidemiology and aetiology

The aetiological and pathogenetic mechanisms of male hypogonadism can be divided into three main categories:

- Primary (hypergonadotropic) hypogonadism due to testicular failure.

- Secondary (hypogonadotropic) hypogonadism caused by insufficient gonadotropin-releasing hormone (GnRH) and/or gonadotropin (FSH, LH) secretion.
- Androgen insensitivity (end-organ resistance).

The most common conditions within these three categories are given in Table 5 (see also Chapter 3.3).

Table 5: Disorders associated with male hypogonadism*

Primary (Hypergonadotropic) hypogonadism (testicular failure)*
Anorchia
Maldescended testes
Klinefelter's syndrome
Y-chromosome microdeletions
Numerical and structural chromosomal anomalies
Trauma, testicular torsion, orchitis
Iatrogenic (surgery, medications, irradiation, or cytostatic drugs)
Exogenous factors (toxins, heat, or occupational hazards)
Systemic diseases (liver cirrhosis, or renal failure)
Testicular tumour
Varicocele
Idiopathic (e.g., late-onset hypogonadism)
Secondary (hypogonadotropic) hypogonadism (secondary testicular failure)
Congenital
Idiopathic hypogonadotropic hypogonadism
Normosmic
Hiposmic/anosmic (Kallmann syndrome)
Acquired (tumours in the following regions)
Diencephalon (craniopharyngioma or meningioma)
Hypothalamus or pituitary
Empty sella syndrome
Granulomatous illnesses
Fractures of the skull base
Ischaemic or haemorrhagic lesions in hypothalamic area
Hyperprolactinaemia
Drugs/anabolic steroids, radiotherapy
Target organ resistance to androgens
Testicular feminisation
Reifenstein syndrome

*Modified from Nieschlag et al. [8].

5.5.2 **Idiopathic hypogonadotropic hypogonadism: aetiology, diagnosis and therapeutic management**

Idiopathic hypogonadotropic hypogonadism is characterised by low levels of gonadotropins and sex steroid in the absence of anatomical or functional abnormalities of the hypothalamic-pituitary-gonadal axis [141]. Idiopathic hypogonadotropic hypogonadism may be an isolated condition or may be associated with anosmia/hyposmia (Kallmann syndrome). Genetic factors causing a deficit of gonadotropins may act at the hypothalamic or pituitary level. Mutations in candidate genes (X-linked or autosomal) can be found in ~30% of congenital cases [141] and should be screened for prior to assisted reproduction [142]. Acquired hypogonadotropic hypogonadism can be caused by some drugs, hormones, anabolic steroids, or tumours.

A suspected tumour requires imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] of the sella region and a complete endocrine work-up. Normal androgen levels and subsequent development of secondary sex characteristics (in cases of onset of hypogonadism before puberty) and a eugonadal state can be achieved by androgen replacement alone. However, stimulation of sperm production requires treatment with human chorionic gonadotropin (hCG) combined with recombinant FSH, urinary FSH or human menopausal gonadotropins (HMGs) [143]. If hypogonadotropic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is pulsatile GnRH [144]. In patients who have developed hypogonadism before puberty and have not been treated with gonadotropins or GnRH, one to two years of therapy may be needed to achieve sperm production.

5.5.3 **Hypergonadotropic hypogonadism: aetiology, diagnosis and therapeutic management**

Many conditions in men with testicular failure are associated with hypergonadotropic hypogonadism (Table 5, see also Chapter 5.2). Most conditions listed in Table 5 only affect the reproductive function of the testes so that only the FSH level is elevated. However, it has been reported that men with infertility are at higher risk for developing impaired Leydig cell function [145], while men with Klinefelter's syndrome often show high LH values and develop hypoandrogenism with ageing [146]. A decrease in testosterone blood concentrations after extensive testicular biopsy in the context of TESE/ICSI has been observed, raising questions about the need for long-term endocrine follow-up of these patients [147]. Laboratory diagnosis of hypergonadotropic hypogonadism is based on a high level of FSH, decreased serum testosterone, and increased LH levels [142]. Testosterone levels should be evaluated in view of the serum concentration of sex hormone binding globulin (SHBG). Based on levels of total testosterone, albumin and SHBG, free and bioavailable testosterone can be calculated. Due to diurnal variation, blood samples for testosterone assessment should be taken before 10.00 am.

Generally, androgen replacement should not be given to men who are considering parenthood or in case of male infertility. Testosterone suppresses pituitary production of LH and FSH, therefore, replacement therapy should not be given for infertility. In obese men, low levels of testosterone may exist due to the conversion of testosterone to oestradiol by the enzyme aromatase [148]. Anti-oestrogens and aromatase inhibitors may help in these patients elevating FSH and LH and potentially increase sperm quality, next to weight reduction. See also EAU Guidelines on Male Hypogonadism [149].

5.5.4 **Recommendations for hypogonadism**

Recommendations	GR
Provide testosterone replacement therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	A
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (human chorionic gonadotropin (hCG), human menopausal gonadotropins (hMG), recombinant follicle-stimulating hormone (rFSH)).	A*
Do not use testosterone replacement for the treatment of male infertility.	A*

*Upgraded following panel consensus.

5.6 **Cryptorchidism**

Cryptorchidism is the most common congenital abnormality of the male genitalia, at one year of age nearly 1% of all full-term male infants have cryptorchidism [150]. Approximately 30% of undescended testes are nonpalpable and may be located within the abdominal cavity. This guideline only deals with the management in adults.

5.6.1 **Aetiology and pathophysiology**

It has been postulated that cryptorchidism may be a part of the so-called testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic influences early in pregnancy. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig cell dysfunction [151].

5.6.1.1 **Pathophysiological effects in maldescended testes**

5.6.1.1.1 **Degeneration of germ cells**

The degeneration of germ cells in maldescended testes is apparent after the first year of life and varies, depending on the position of the testis [152]. During the second year, the number of germ cells declines. Early treatment is therefore recommended (after the age of six months surgery should be performed within the subsequent year with age eighteen months the latest) to conserve spermatogenesis and hormone production, as well as to decrease the risk for tumours [153]. Surgical treatment is the most effective. Medical treatment with GnRH may be beneficial but long-term follow-up data are required. It has been reported that hCG treatment may be harmful to future spermatogenesis therefore, the Nordic Consensus Statement on treatment of undescended testes does not recommend it on a routine basis [154]. See also EAU Guidelines on Paediatric Urology [155].

5.6.1.1.2 **Relationship with fertility**

Semen parameters are often impaired in men with a history of cryptorchidism [156]. Early surgical treatment may have a positive effect on subsequent fertility [157]. In men with a history of unilateral cryptorchidism,

paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%). In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity is only 35-53% [158].

5.6.1.1.3 Germ cell tumours

As a component of the Testicular Dysgenesis Syndrome cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcification and intratubular germ cell neoplasia of unclassified type (ITGCNU); formerly carcinoma *in situ* (CIS) of the testes. In 5-10% of testicular cancers, there is a history of cryptorchidism [159]. The risk of a germ cell tumour (GCT) is 3.6-7.4 times higher than in the general population and 2-6% of men with a history of cryptorchidism will develop a testicular tumour [150]. Orchidopexy performed before the age of puberty has been reported to decrease the risk of testicular cancer [160].

5.6.2 Disease management

5.6.2.1 Hormonal treatment

Human chorionic gonadotropin or GnRH is not recommended for the treatment of cryptorchidism in adulthood.

5.6.2.2 Surgical treatment

In adolescence removal of intra-abdominal testis (with a normal contralateral testis) can be recommended, because of the theoretical risk of later malignancy [161]. In adulthood, a palpable undescended testis should not be removed because it still produces testosterone. Furthermore, as indicated above, correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men [158]. Vascular damage is the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In men with non-palpable testes, the post-operative atrophy rate was 12% in those cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged orchidopexy has been reported in up to 40% of patients [162]. At the time of orchidopexy, performed in adulthood, testicular biopsy for detection of ITGCNU is recommended. At the time of orchiectomy in the treatment of germ cell tumours biopsy of the contralateral testis should be offered to patients at high risk for ITGCNU (i.e. history of cryptorchidism, < 12 ml. testicular volume, poor spermatogenesis [163]).

5.6.3 Summary of evidence recommendations for cryptorchidism

Summary of evidence	LE
Cryptorchidism is multifactorial in origin and can be caused by genetic factors and endocrine disruption early in pregnancy.	2a
Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility and germ cell tumours.	2b
Paternity in men with unilateral cryptorchidism is almost equal to that in men without cryptorchidism.	3
Bilateral cryptorchidism significantly reduces the likelihood of paternity.	3

Recommendations	GR
Do not use hormonal treatment of cryptorchidism in adults.	A
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy for detection of intratubular germ cell neoplasia of unclassified type (ITGCNU) (formerly carcinoma <i>in situ</i> (CIS)).	B

5.7 Idiopathic male infertility

No demonstrable cause of infertility is found in at least 44% of infertile men [164].

5.7.1 Disease management

5.7.1.1 Empirical treatments

A wide variety of empirical drug treatments of idiopathic male infertility have been used. However, there is little scientific evidence for an empirical approach [165]. Clomiphen citrate and tamoxifen have been widely used in idiopathic OAT: a recent meta-analysis reported some improvement in sperm quality and spontaneous pregnancy rates [166]. Androgens, bromocriptine, α -blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. Although gonadotrophins (HMG/rFSH) might be beneficial in regards to pregnancy rates and live birth in idiopathic male factor subfertility, however, their use should be cautious given the high risk of bias and heterogeneity of available studies [167]. Men taking oral antioxidants had an associated significant increase in sperm parameters [168] and in live birth rates in IVF

patients in a Cochrane analysis [169]. Concerning natural conception the role of antioxidants needs further investigations [170].

5.7.2 **Recommendation for idiopathic male infertility**

Recommendations	GR
Medically treat male infertility only for cases of hypogonadotropic hypogonadism.	A
No clear recommendation can be made for treatment with gonadotropins, anti-oestrogens and antioxidants even for a subset of patients.	B

5.8 **Male contraception**

Development of male contraceptive methods is important because up to 40% of women have an unmet need for family planning, with approximately 80 million women every year having unintended or unwanted pregnancies [171]. Three of the four methods of male contraception have been in use for hundreds of years (i.e., condoms, periodic abstinence, and withdrawal). The typical first-year failure rates of traditional male methods are high (withdrawal 19%, periodic abstinence 20%, and condoms 3-14%) compared to the failure rates of 0.1-3% for modern reversible female methods [172]. For men, male contraceptive methods must be acceptable, cheap, reversible, and effective. The method nearest to being generally available clinically is hormonal male contraception, which is based on the suppression of gonadotropins and testosterone substitution to maintain male sexual function and bone mineralisation, and to prevent muscle wasting [173]. Various contraceptive regimens have been developed and tested, including testosterone monotherapy, androgen/progestin combinations, testosterone with GnRH analogues, and selective androgen- and progestinreceptor modulators [174]. There are racial differences in the response to androgens alone. However, a combination of testosterone with progestin results in complete suppression of spermatogenesis in all races, and provides contraceptive efficacy equivalent to female hormonal methods [175].

5.8.1 **Vasectomy**

Vasectomy is an effective method of permanent male surgical sterilisation [168]. Extensive guidelines on vasectomy were published by the EAU in 2012 [2]. Before vasectomy, the couple should be fully informed about the benefits and risks, especially as an Australian telephone survey found that 9.2% of respondents regretted having a vasectomy [176].

5.8.1.1 *Surgical techniques*

Various techniques are available for vasectomy. The least invasive approach is no-scalpel vasectomy which is also associated with a low rate of complications [177, 178]. The most effective occlusion technique is cauterisation of the lumen of the vas deferens and fascial interposition [179-181]. Most techniques can be carried out safely under local anaesthesia in an outpatient clinic.

5.8.1.1.1 **Complications**

Vasectomy does not significantly alter spermatogenesis and Leydig cell function. The volume of ejaculate remains unchanged. Potential systemic effects of vasectomy, including atherosclerosis, have not been proven, and there is no evidence of a significant increase in any systemic disease after vasectomy. An increased rate of prostate cancer in men who underwent vasectomy has not been detected [182, 183]. Acute local complications associated with vasectomy include haematoma, wound infection, and epididymitis in up to 5% of cases [182]. The potential long-term complications (e.g., chronic testicular pain) [184] must be discussed with the patient before the procedure.

5.8.1.1.2 **Vasectomy failure**

If an effective occlusion technique is used, the risk of recanalisation after vasectomy should be < 1% [185]. However, patients should be informed pre-operatively that, although rare, long-term recanalisation might occur [186]. No motile spermatozoa should be detected three months after vasectomy. Persistent motility is a sign of vasectomy failure, and the procedure will need to be repeated. A "special clearance" given by the urologist with non-motile spermatozoa < 100,000/mL is still under discussion [187].

5.8.2 **Counselling**

Counselling with regard to vasectomy must address the following aspects:

- Vasectomy should be considered irreversible,
- Vasectomy is associated with a low complication rate; however, because it is an elective operation, even small risks must be explained, because men (and their partners) might wish to consider these before giving consent,

- Vasectomy can fail, although the failure rate is low,
- Couples should be advised to continue with other effective contraception until clearance is confirmed,
- All available data indicate that vasectomy is not associated with any serious, long-term, side-effects [188],
- Vasectomy involving cauterisation and fascial interposition appears to be the most effective technique in the prevention of early recanalisation [179, 185, 189].

5.8.3 **Vasectomy reversal**

A wide range of surgical success rates have been published for vasectomy reversal (up to 90%), depending on the time between vasectomy and re-fertilisation, type of vasectomy (e.g., open-ended or sealed), type of reversal (vasovasostomy or vasoepididymostomy), and whether reversal was unilateral or bilateral. Microsurgical techniques should be used [190].

5.8.3.1 *Length of time since vasectomy*

Vasovasostomy results have shown patency rates up to 90%. The longer the interval is from vasectomy to reversal, the lower the pregnancy rate is. In a study of 1,469 men who had undergone microsurgical vasectomy reversal, patency and pregnancy rates were 97% and 76%, respectively, for an interval up to three years after vasectomy; 88% and 53% for three to eight years, 79% and 44% for nine to fourteen years, and 71% and 30% for > fifteen years [191].

5.8.3.2 *Tubulovasostomy*

The chance of secondary epididymal obstruction after vasectomy increases with time. After an interval of ten years, 25% of men appear to have epididymal blockage. If secondary epididymal obstruction occurs, tubulovasostomy is needed to reverse the vasectomy (see Chapter 5.3) [192].

5.8.3.3 *Microsurgical vasectomy reversal vs. epididymal or testicular sperm retrieval and ICSI*

According to the calculations of cost per delivery for vasectomy reversal vs. sperm retrieval/ICSI, under a wide variety of initial assumptions, it is clear that vasectomy reversal is associated with a considerably lower cost per delivery and higher delivery rates [80, 113, 193, 194]. Sperm retrieval and ICSI must yield an 81% pregnancy rate per cycle to achieve equal costs to vasectomy reversal.

5.8.4 *Summary of evidence and recommendations for male contraception*

Summary of evidence	LE
Vasectomy meets best the criteria for male contribution to permanent contraception, with regard to efficacy, safety and side effects.	1a
All available data indicate that vasectomy is not associated with any serious, long-term side-effects.	1b
Microsurgical vasectomy reversal is a low-risk and cost-effective method of restoring fertility.	1a
Methods of male contraception other than vasectomy are associated with high failure rates or are still experimental (e.g., hormonal approach).	3

Recommendations	GR
Cauterisation and fascial interposition are the most effective techniques for the prevention of early recanalisation.	A
Inform patients seeking vasectomy about the surgical method, risk of failure, potential irreversibility, the need for post-procedure contraception until clearance, and the risk of complications.	A*
To achieve pregnancy, microsurgical epididymal sperm aspiration (MESA)/ percutaneous epididymal sperm aspiration (PESA)/testicular sperm extraction (TESE) - together with intracytoplasmic sperm injection (ICSI) is a second-line option for men who decline a vasectomy reversal and those with failed vasectomy reversal surgery.	B

*Upgraded following panel consensus

5.9 **Male accessory gland infections and infertility**

5.9.1 **Introduction**

Infections of the male urogenital tract are potentially curable causes of male infertility [121, 195, 196]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [121]. However, specific data are not available to confirm that these diseases have a negative influence on sperm quality and male fertility in general.

5.9.2 **Diagnostic evaluation**

5.9.2.1 *Ejaculate analysis*

Ejaculate analysis (see Chapter 4.2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information about sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome (CP/CPPS) (NIH IIa vs. NIH 3b National Institutes of Health classification for CP/CPPS).

5.9.2.2 *Microbiological findings*

After exclusion of urethritis and bladder infection, $>10^6$ peroxidase-positive white blood cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In this case, a culture should be performed for common urinary tract pathogens. A concentration of $>10^3$ cfu/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia. The sampling time can influence the positive rate of microorganisms in semen and the frequency of isolation of different strains [197]. The ideal diagnostic test for *Chlamydia trachomatis* in semen has not yet been established [198]. In contrast to serological findings in women, antibody tests for *C. trachomatis* in seminal plasma are not indicative if no type-specific methods are used [198]. *Ureaplasma urealyticum* is pathogenic only in high concentrations ($>10^3$ cfu/mL ejaculate). No more than 10% of samples analysed for ureaplasma exceed this concentration [199]. Normal colonisation of the urethra hampers the clarification of mycoplasma-associated urogenital infections, using samples such as the ejaculate [200].

5.9.2.3 *White blood cells*

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [201]. Infection is indicated only by an increased level of leukocytes. Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections [202]. According to the WHO classification, leukocytospermia is defined as $>10^6$ WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis [203, 204]. Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH 3B).

5.9.2.4 *Sperm quality*

The deleterious effects of chronic prostatitis on sperm density, motility and morphology are under debate [196]. All investigations have given contradictory results, and have not confirmed that chronic prostatitis has a decisive role in altering conventional semen parameters [205-207].

5.9.2.5 *Seminal plasma alterations*

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [196, 208, 209], with a suggested cut-off level of approximately 600 ng/mL [194]. Various cytokines are involved in inflammation and can influence sperm function. Several studies have investigated the association between interleukin (IL) concentration, leukocytes, and sperm function [210-212], but no correlations have been found. The prostate is the main site of origin of IL-6 and IL-8 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male accessory gland inflammatory process [213]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion (EPS) [214].

5.9.2.6 *Glandular secretory dysfunction*

Infections of the sex glands can impair their excretory function. Decreased quantities of citric acid, phosphatase, fructose, zinc, and α -glutamyl-transferase activity are indicators of disturbed prostatic secretory parameters [196]. Reduced fructose concentration indicates impaired vesicular function [199, 215].

5.9.2.7 *Reactive oxygen species*

Reactive oxygen species might be increased in chronic urogenital infections associated with increased leukocyte numbers [216]. However, their biological significance in prostatitis remains unclear [196].

5.9.2.8 *Disease management*

Treatment of chronic prostatitis is usually targeted at relieving symptoms [217, 218]. The aims of therapy for altered semen composition in male adnexitis are:

- reduction or eradication of microorganisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g., leukocytes) and secretory parameters;
- improvement of sperm parameters to counteract fertility impairment [219].

Only antibiotic therapy of chronic bacterial prostatitis (NIH II according to the classification) has provided symptomatic relief, eradication of microorganisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. Although antibiotics might improve sperm quality [219], there is no evidence that treatment of chronic prostatitis increases the probability of conception [196, 220].

5.9.3 Epididymitis

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men < 35 years of age, epididymitis is most often caused by *C. trachomatis* or *Neisseria gonorrhoea* [221, 222]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with urinary tract infection and occurs more often in men aged > 35 years [223].

5.9.3.1 Diagnostic evaluation

5.9.3.1.1 Ejaculate analysis

Ejaculate analysis according to WHO criteria, might indicate persistent inflammatory activity. Transiently decreased sperm counts and forward motility are observed [221, 224, 225]. Semen culture might help to identify pathogenic microorganisms. Development of stenosis in the epididymal duct, reduction of sperm count, and azoospermia are more important in the follow-up of bilateral epididymitis (see Chapter 5.3).

5.9.3.1.2 Disease management

Antibiotic therapy is indicated before culture results are available.

Treatment of epididymitis results in:

- microbiological cure of infection;
- improvement of clinical signs and symptoms;
- prevention of potential testicular damage;
- prevention of transmission;
- decrease of potential complications (e.g., infertility or chronic pain).

Patients with epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* must be told to refer their sexual partners for evaluation and treatment [226].

5.9.4 Summary of evidence and recommendation for male accessory gland infections

Summary of evidence	LE
Urethritis and prostatitis are not clearly associated with male infertility.	3
Antibiotic treatment often only eradicates microorganisms; it has no positive effect on inflammatory alterations and cannot reverse functional deficits and anatomical dysfunction.	2a
Although antibiotic treatment for MAGI might provide improvement in sperm quality, it does not necessarily enhance the probability of conception.	2a

Recommendation	GR
Instruct patients with epididymitis that is known or suspected to be caused by <i>N. gonorrhoeae</i> or <i>C. trachomatis</i> to refer their sexual partners for evaluation and treatment.	B

5.10 Germ cell malignancy and testicular microcalcification

5.10.1 Germ cell malignancy and male infertility

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years, and affects approximately 1% of subfertile men. The lifetime risk of TGCT varies between ethnic groups and countries. The highest annual incidence of TGCT occurs in Caucasians, and varies from 10/100,000 (e.g., in Denmark and Norway) to 2/100,000 (e.g., in Finland and the Baltic countries). Generally, seminomas and nonseminomas are preceded by CIS, and untreated ITGCNU will eventually progress to invasive cancer [227, 228]. The most convincing evidence for a general decline in male reproductive health is the increase in testicular cancer seen in western countries [229, 230]. In almost all countries with reliable cancer registers, the incidence of testicular cancer has increased [66, 231]. Cryptorchidism and hypospadias are associated with an increased risk of testicular cancer; men with cryptorchidism and/or hypospadias are over-represented among patients with testicular cancer. Men with dysgenetic testes have an increased risk of developing testicular cancer in adulthood. These cancers arise from premalignant gonocytes or CIS cells [232]. Testicular microlithiasis (TM), seen on US, can be associated with GCT and CIS of the testes.

5.10.2 Testicular germ cell cancer and reproductive function

Men with TGCT have decreased semen quality, even before cancer is diagnosed [233]. Orchidectomy implies a risk of azoospermia in these men, with sperm found in the ejaculate before the tumour-bearing testis has been removed. Semen cryopreservation before orchidectomy should therefore be considered (see Chapter 5.12).

Treatment of TGCT can result in additional impairment of semen quality [234]. In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [235]. The risk of hypogonadism may therefore be increased in men treated for TGCT. The measurement of pre-treatment levels of testosterone, SHBG, LH and oestradiol might help to anticipate post-treatment hypogonadism. Men who have had TGCT and have low normal androgen levels should receive long-term follow-up because they are at risk of developing hypogonadism as a result of an age-related decrease in testosterone production [236]. The risk of hypogonadism is most pronounced in TGCT patients treated with > three cycles of chemotherapy or irradiation of retroperitoneal lymph nodes. However, this risk is greatest at six to twelve months post-treatment. This suggests there may be some improvement in Leydig cell function, and why it is reasonable to expect initiation of androgen replacement, until the patient shows continuous signs of testosterone deficiency, even at two years follow-up [227]. The risk of low libido and erectile dysfunction is also increased in TGCT patients [237]. In case of azoospermia, testicular sperm may be recovered to safeguard patient's fertility (Onco-TESE) [238].

5.10.3 **Testicular microlithiasis (TM)**

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular US [239-241]. Although the true incidence of microcalcification in the general population is unknown, it is probably rare. However, US findings of TM are common in men with TGCT, cryptorchidism, testicular dysgenesis, infertility, testicular torsion and atrophy, Klinefelter's syndrome, hypogonadism, male pseudoherma-phroditism, varicocele, epididymal cysts, pulmonary microlithiasis, and non-Hodgkin's lymphoma. The incidence reported seems to be higher with high-frequency US machines [242]. The relationship between TM and infertility is unclear, but probably relates to dysgenesis of the testes, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification occurs. Testicular microlithiasis is found in testes at risk of malignant development. The reported incidence of TM in men with TGCT is 6-46% [243-245]. TM should therefore be considered premalignant. Testicular biopsies from men with TM have found a higher prevalence of CIS, especially in those with bilateral microlithiasis [246]. However, TM is found most often in men with a benign testicular condition and the microcalcification itself is not malignant. Further investigation of the association between TM and CIS will require testicular biopsies in large series of men without signs of TGCT. However, available data indicate that men in whom TM is found by US, and who have an increased risk of TGCT, should be offered testicular biopsy for detection of CIS. The list of high-risk patients includes men with infertility and bilateral TM, atrophic testes, undescended testes, a history of TGCT, and contralateral TM [230].

5.10.4 **Recommendations for germ cell malignancy and testicular microcalcification**

Recommendations	GR
As for all men, encourage patients with testicular microlithiasis (TM) and without special risk factors (see below) to perform self-examination because this might result in early detection of testicular germ cell tumour (TGCT).	B
Do not perform testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic computed tomography (CT), in men with isolated TM without associated risk factors (e.g. infertility, cryptorchidism, testicular cancer, and atrophic testis).	B
Perform testicular biopsy for men with TM, who belong to one of the following high-risk groups: infertile and bilateral TM, atrophic testes, undescended testes, a history of TGCT.	B
If there are suspicious findings on physical examination or ultrasound in patients with TM and associated lesions, perform surgical exploration with testicular biopsy or orchidectomy.	B
Follow men with TGCT because they are at increased risk of developing hypogonadism and sexual dysfunction.	B

5.11 **Disorders of ejaculation**

Disorders of ejaculation are uncommon, but important causes of male infertility.

5.11.1 **Classification and aetiology**

5.11.1.1 *Anejaculation*

Anejaculation involves complete absence of antegrade or retrograde ejaculation. It is caused by failure of semen emission from the seminal vesicles, prostate and ejaculatory ducts into the urethra [247]. True anejaculation is usually associated with a normal orgasmic sensation. True anejaculation is always associated with central or peripheral nervous system dysfunction or with drugs [248] (Table 6).

5.11.1.2 Anorgasmia

Anorgasmia is the inability to reach orgasm and can give rise to anejaculation. Anorgasmia is often a primary condition and its cause is usually psychological.

5.11.1.3 Delayed ejaculation

In delayed ejaculation, abnormal stimulation of the erect penis is needed to achieve orgasm with ejaculation [247]. Delayed ejaculation can be considered a mild form of anorgasmia. The causes of delayed ejaculation can be psychological, organic (e.g. incomplete spinal cord lesion [249] or iatrogenic penile nerve damage [250]), or pharmacological (e.g. selective serotonin re-uptake inhibitors (SSRIs), antihypertensives, or antipsychotics) [251].

5.11.1.4 Retrograde ejaculation

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation as a result of semen passing backwards through the bladder neck into the bladder. Patients experience a normal or decreased orgasmic sensation. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, urethral, or bladder neck incompetence (Table 6).

Table 6: Aetiology of anejaculation and retrograde ejaculation

Neurogenic	Pharmacological
Spinal cord injury	Antihypertensives
Cauda equina lesions	α 1-adrenoceptor antagonists
Multiple sclerosis	Antipsychotics and antidepressants
Autonomic neuropathy (diabetes mellitus)	Alcohol
Retroperitoneal lymphadenectomy	
Sympathectomy or aortoiliac surgery	
Colorectal and anal surgery	
Parkinson's disease	
Urethral	Bladder neck incompetence
Ectopic ureterocele	Congenital defects/dysfunction of hemitrigone
Urethral stricture	Bladder extrophy
Urethral valves or verumontanum hyperplasia	Bladder neck resection (transurethral resection of the prostate)
Congenital dopamine β -hydroxylase deficiency	Prostatectomy

5.11.1.5 Asthenic ejaculation

Asthenic ejaculation is characterised by an altered propulsive phase, with a normal emission phase [251]. The orgasmic sensation is reduced and the typically rhythmical contractions associated with ejaculation are missing. Asthenic ejaculation does not usually affect semen quality.

5.11.1.6 Premature ejaculation

The International Society for Sexual Medicine (ISSM) has adopted the first evidence-based definition of lifelong premature ejaculation (PE): "Premature ejaculation is a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy". Premature ejaculation may be strictly organic (e.g., prostatitis-related) or psychogenic, partner-related or non-selective, and can be associated with erectile dysfunction. It does not impair fertility, provided intravaginal ejaculation occurs.

5.11.2 Diagnostic evaluation

Diagnostic management includes the following recommended procedures.

5.11.2.1 Clinical history

The patient must be carefully checked for diabetes, neuropathy, trauma, urogenital infection, previous surgery, and medication. Particular attention must be paid to the characteristics of micturition and ejaculation (presence of nocturnal emission, ejaculatory ability in given circumstances, and primary or acquired disorder), as well as to psychosexual aspects.

5.11.2.2 *Physical examination*

Genital and rectal examinations are conducted, including evaluation of the prostate, bulbocavernosus reflex and anal sphincter tone.

5.11.2.3 *Post-ejaculatory urinalysis*

Post-ejaculatory urinalysis of centrifuged urine can be used to determine if there is total or partial retrograde ejaculation.

5.11.2.4 *Microbiological examination*

Initial, mid-stream urine, expressed prostatic secretion, and/or urine after prostatic massage are cultured for evidence of prostatic infection. In cases of increased leukocytes in semen, semen culture or biochemical infection marker tests are also suggested [252].

5.11.2.5 *Optional diagnostic work-up*

This diagnostic work-up can include:

- neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked potentials);
- tests for autonomic neuropathy;
- psychosexual evaluation;
- videocystometry;
- cystoscopy;
- transrectal ultrasonography;
- uroflowmetry;
- vibratory stimulation of the penis.

5.11.3 ***Disease management***

Infertility caused by disorders of ejaculation is seldom treated on the basis of aetiology. Treatment usually involves retrieval of spermatozoa for use in assisted reproduction techniques (ARTs). The following aspects must be considered when selecting treatment:

- age of patient and his partner;
- psychological problems of the patient and his partner;
- couple's willingness and acceptance of different fertility procedures;
- associated pathology;
- psychosexual counselling.

5.11.3.1 *Aetiological treatment*

If possible, any pharmacological treatment that is interfering with ejaculation should be stopped. In painful ejaculation, tamsulosin can be administered during antidepressant treatment [253]. Treatment should be given for urogenital infections (i.e., in case of painful ejaculation) [252]. Dapoxetine is an SSRI that has been introduced for the therapy of PE [254], because it appears that PE is related to serotonin levels. Psychotherapy is usually not very effective.

5.11.3.2 *Symptomatic treatment*

5.11.3.2.1 *Premature ejaculation*

Premature ejaculation can be treated with the SSRI dapoxetine or topical anaesthetic agents to increase intravaginal ejaculation latency time, behavioural therapy, and/or psychotherapy.

5.11.3.2.2 *Retrograde ejaculation*

In the absence of spinal cord injury, anatomical anomalies of the urethra, or pharmacological agents, drug treatment must be used to induce antegrade ejaculation (Table 7). Alternatively, the patient can be encouraged to ejaculate when his bladder is full to increase bladder neck closure [255].

Table 7: Drug therapy for retrograde ejaculation

Drug	Dosage regimen	Ref.
Ephedrine sulphate	10-15 mg four times daily	[256]
Pseudoephedrine	60 mg four times daily	[257]
Midodrine	7.5–15 mg daily	[257]
Imipramine	25 mg twice daily	[257]
Brompheniramine maleate	8 mg twice daily	[258]
Desipramine	50 mg every second day	[259]

Sperm collection from post-orgasmic urine for use in ART is recommended if:

- drug treatment is ineffective or intolerable as a result of side-effects;
- the patient has a spinal cord injury;
- drug therapy inducing retrograde ejaculation cannot be interrupted.

If the biological sperm preparation is not of sufficient quality for intrauterine insemination, the couple must undergo in vitro reproductive procedures (e.g. ICSI). In the case of insufficient drug therapy, testicular (TESE or PESA) or epididymal (MESA) sperm retrieval techniques can be used for assisted reproduction.

5.11.3.2.3 Anejaculation

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia is not very effective. In all these cases, and in men who have a spinal cord injury, vibrostimulation (i.e., application of a vibrator to the penis) is first-line therapy. In anejaculation, vibrostimulation evokes the ejaculation reflex [260], which requires an intact lumbosacral spinal cord segment. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an IVF programme. If vibrostimulation has failed, electro-ejaculation can be the therapy of choice [261]. When electro-ejaculation fails or cannot be carried out, sperm can be retrieved from the seminal ducts by aspiration from the vas deferens [262] (see Chapter 5.3) or seminal tract washout [263]. TESE can then be used [252, 264]. Anejaculation following either surgery for testicular cancer or total mesorectal excision can be prevented using monolateral lymphadenectomy or autonomic nerve preservation [264], respectively.

5.11.4 Summary of evidence and recommendations for disorders of ejaculation

Summary of evidence	LE
Ejaculation disorders can be treated using a wide range of drugs and physical stimulation (eg vibratory stimulation), with a high level of efficacy.	3
Pharmacotherapy includes either dapoxetine on demand (a short-acting SSRI that is the only approved pharmacological treatment for PE) or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing. Alternatively use topical anaesthetics (LE: 1b) or tramadol (LE: 2a).	1a
In men with spinal cord injury, vibrostimulation and/or electro-ejaculation are effective methods of sperm retrieval.	2

Recommendations	GR
Offer aetiological treatments for ejaculatory disorders before performing sperm collection and assisted reproduction technique (ART).	B
To treat disorders of ejaculation, offer pharmacological treatment of either dapoxetine on demand (a short-acting selective serotonin reuptake inhibitors (SSRI) that is the only approved pharmacological treatment for premature ejaculation), or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing.	A
Alternatively offer topical anaesthetics or tramadol.	A

5.12 Semen cryopreservation

Cryopreservation is the storage of biological material at sub-zero temperatures [e.g., -80 or -196°C (the boiling point of liquid nitrogen)], at which the biochemical processes of cell metabolism are slowed or interrupted. At -196°C, the biochemical reactions that lead to cell death are stopped.

5.12.1 *Indications for storage*

Storage of sperm is available in many clinics for the following indications:

before potentially sterilising chemotherapy or radiotherapy for cancer (onco-TESE) or for non-malignant diseases [265];

- before surgery that might interfere with fertility (e.g. bladder neck surgery in a younger man or removal of a testicle in a man with testicular malignancy, or before vasectomy or transgender surgery);
- for men with progressive decrease in semen quality as a result of diseases that have an associated risk of subsequent azoospermia (i.e., pituitary macroadenoma, craniopharyngioma, empty sella syndrome, chronic nephropathy, uncontrolled diabetes mellitus, and multiple sclerosis);
- for men with paraplegia when sperm have been obtained by electro-ejaculation or obtained by penile vibratory stimulation;
- for men with psychogenic anejaculation, after sperm have been obtained either by electro-ejaculation or a sperm retrieval procedure;
- after gonadotropin treatment has induced spermatogenesis in men with hypogonadotropic hypogonadism;
- for men with NOA, the chance of finding sperm using micro-TESE is ~50%.

Cryopreservation can be used for sperm collected through TESE, avoiding repeated sperm retrieval procedures and unnecessary hyperstimulation of the female partner:

- in any situation in which sperm have been obtained by a sperm retrieval procedure (e.g., after failed vasectomy reversal, or in some cases of epididymal obstruction not amenable to surgery);
- for storage of donor sperm, because cryopreservation reduces the risk of transmission of infection from sperm donors. According to the European directives 2004/23 EC and 2006/17 EC fresh sperm are no longer to be used for non-partner donations.

5.12.2 *Precautions and techniques*

5.12.2.1 *Freezing and thawing process*

The cryopreservation techniques currently used are not yet optimal because damage occurs to cells during cryopreservation and prolonged storage. Most damage occurs during freezing and thawing. Major causes of damage during freezing are ice crystal formation and cell dehydration, which disrupt the cell wall and intracellular organelles. Sperm morphology, motility and vitality decrease significantly after thawing, and cryopreservation increases the damage done to sperm DNA [266-269]. Further damage can be caused by contamination of samples with microorganisms and high levels of superoxide radicals [270, 271]. To reduce ice crystal formation, a cryopreservation solution is added before freezing. Various cryopreservation solutions are available commercially, most of which contain varying proportions of glycerol and albumin. After freezing, the samples are immersed in liquid nitrogen.

Several techniques have been developed to try to reduce damage caused by freezing and thawing, including:

- one-step freezing method [272, 273]: sample is held in the vapour phase for ten minutes before being plunged into liquid nitrogen;
- slow or multi-step method [274]: sample is gradually cooled in the vapour phase for approximately 40 minutes. A programmable automatic freezing machine, which is preset to cool at a rate of 1-10°C per minute is used.

The method available depends on the resources of the laboratory. Whichever freezing technique is used, it should be tested using donor sperm and post-thaw examination, and should regularly undergo a quality-control programme. The likelihood of sperm survival decreases with repeated freezing and thawing. The maximum viable storage time for human sperm is not known.

5.12.2.2 *Cryopreservation of small numbers of sperm*

Standard cryopreservation in straws is an efficient way of storing large numbers of sperm (e.g., for a donor insemination programme). However, in micro-TESE, few sperm might be obtained, and the choice is either to freeze testicular tissue and find sperm after thawing the tissue, or to freeze small numbers of sperm. If sperm are frozen in straws, it can be difficult to find any sperm after thawing. Instead, the sperm should be frozen in a pellet [275] or in a container [276].

5.12.2.3 *Testing for infections and preventing cross-contamination*

Sperm storage in straws is used extensively. Large numbers of straws are stored in canisters, with the straws being bathed in a pool of liquid nitrogen. Microbial contamination of the pool of liquid nitrogen results in contamination of the outside of all the straws [277]. The most widely used safeguard is to use so-called

high security closed straws. According to the European directives 2004/23 and 2006/17, samples should be tested for hepatitis B and C and human immunodeficiency virus (HIV). In case of non-partner donation, samples are also tested for *C. Trachomatis* (by Nucleic Acid Testing [NAT]) and syphilis, as well as genetics, that is, karyotype and most prevalent genetic disorders in the population to which the non-partner donor belongs. Until the test results are known, samples must be stored in an individual quarantine vessel (separate storage). If open straws are used (e.g., for vitrification purposes) some laboratories use the additional safeguard of doublewrapping the straws before freezing, although this is more costly. Some centres carry out cytomegalovirus testing and store negative and positive samples separately. Considerable ethical issues surround the storage of samples before cancer chemotherapy in men who are hepatitis-virus- or HIV-positive. Few clinics have separate storage facilities for HIV-positive samples. However, the success of antiretroviral treatment is increasing the number of HIV-positive men who may wish to store sperm. There is also concern about HIV transmission to children conceived using HIV-positive sperm, because sperm-washing techniques fail in ~5% of cases.

5.12.2.4 *Fail-safe precautions to prevent loss of stored materials*

Any laboratory that undertakes long-term storage of human biological materials should have procedures that guard against accidental loss of material caused by storage vessel failure. This is particularly important for sperm stored before potentially sterilising cancer chemotherapy, because these patients may not be able to obtain further sperm.

5.12.2.5 *Orphan samples*

In malignancy and some other situations, several years might pass before stored samples are required. Inevitably, during this time, the owners of some samples might disappear or die, leaving behind orphan samples for which the owner is no longer contactable. The duty of the laboratory and the legal ownership of these samples can create considerable problems.

5.12.3 **Biological aspects**

Cryopreservation induces deterioration of semen quality. After the sample has been thawed, motility [278] and morphology [279, 280] are worsened, including mitochondrial acrosomal and sperm tail damage [262]. Sperm freezing decreases motility by 31% and mitochondrial activity by 36%, and causes morphological disruption in 37% of sperm [273]. Motility is correlated best with IVF capacity of the thawed sample. Further improvement can be achieved by selecting the subpopulation of sperm with the best motility and DNA integrity and freezing these sperm in seminal plasma [275].

5.12.4 **Summary of evidence and recommendations for semen cryopreservation**

Summary of evidence	LE
The purpose of sperm cryopreservation is to enable future assisted reproduction technique procedures.	1b
Cryopreservation techniques are not optimal, and future efforts are needed to improve the outcome of sperm banking.	3

Recommendations	GR
Offer cryopreservation of semen to all men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders.	A
Offer simultaneous sperm cryopreservation if testicular biopsies will be performed for fertility diagnosis.	A
If cryopreservation is not available locally, inform patients about the possibility of visiting, or transferring to a cryopreservation unit before therapy starts.	C
Take precautions to prevent transmission of viral, sexually transmitted or any other infection by cryostored materials from donor to recipient, and to prevent contamination of stored samples. These precautions include testing of the patient and the use of rapid testing and quarantine of samples until test results are known. Do not store samples from men who are positive for hepatitis virus or HIV in the same container as samples from men who have been tested and are free from infection.	C

6. REFERENCES

1. Dohle, G.R., et al. EAU guidelines on male infertility. *Eur Urol*, 2005. 48: 703.
<https://www.ncbi.nlm.nih.gov/pubmed/16005562>
2. Dohle, G.R., et al. European Association of Urology guidelines on vasectomy. *Eur Urol*, 2012. 61: 159.
<https://www.ncbi.nlm.nih.gov/pubmed/22033172>
3. Jungwirth, A., et al. European Association of Urology guidelines on Male Infertility: the 2012 update. *Eur Urol*, 2012. 62: 324.
<https://www.ncbi.nlm.nih.gov/pubmed/22591628>
4. Bob Philips, C.B., Dave Sackett, Doug Badenouch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. . Modified from Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009). Updated Jeremy Howick March 2009. Access date February 2014.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
5. Bruins M., et al. What is the effectiveness and harm of medical and/or nutritional therapy on the pregnancy rate in couples with idiopathic male infertility? PROSPERO: International prospective register of systematic reviews, 2016.
http://www.crd.york.ac.uk/prospero/display_record.asp?src=trip&ID=CRD42016032976
6. WHO, WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple. 2000, Cambridge University Press: Cambridge.
<http://www.who.int/reproductivehealth/publications/infertility/9780521431361/en/>
7. Greenhall, E., et al. The prevalence of subfertility: a review of the current confusion and a report of two new studies. *Fertil Steril*, 1990. 54: 978.
<https://www.ncbi.nlm.nih.gov/pubmed/2245856>
8. Andrology, In: Nieschlag E, Behre HM and Nieschlag S (eds). Male reproductive health and dysfunction, in Male reproductive health and dysfunction. 2010, Springer Verlag: Berlin.
9. Snick, H.K., et al. The spontaneous pregnancy prognosis in untreated subfertile couples: the Walcheren primary care study. *Hum Reprod*, 1997. 12: 1582.
<https://www.ncbi.nlm.nih.gov/pubmed/9262301>
10. Rowe, T. Fertility and a woman's age. *J Reprod Med*, 2006. 51: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/16674009>
11. Lotti, F., et al. Ultrasound of the male genital tract in relation to male reproductive health. *Human Reproduction Update*, 2015. 21 (1) (pp 56-83).
<https://www.ncbi.nlm.nih.gov/pubmed/25038770>
12. WHO, WHO Laboratory Manual for the Examination and Processing of Human Semen, in 5th edn. 2010.
<http://www.who.int/reproductivehealth/publications/infertility/9789241547789/en/>
13. Hauser, R., et al. Fertility in cases of hypergonadotropic azoospermia. *Fertil Steril*, 1995. 63: 631.
<https://www.ncbi.nlm.nih.gov/pubmed/7851598>
14. Martin-du-Pan, R.C., et al. Increased follicle stimulating hormone in infertile men. Is increased plasma FSH always due to damaged germinal epithelium? *Hum Reprod*, 1995. 10: 1940.
<https://www.ncbi.nlm.nih.gov/pubmed/8567817>
15. Abdel-Meguid, T.A. Predictors of sperm recovery and azoospermia relapse in men with nonobstructive azoospermia after varicocele repair. *J Urol*, 2012. 187: 222.
<https://www.ncbi.nlm.nih.gov/pubmed/22100001>
16. Colpi, G.M., et al. Sperm retrieval for intra-cytoplasmic sperm injection in non-obstructive azoospermia. *Minerva Urol Nefrol*, 2005. 57: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/15951734>
17. Kim, E.D., et al. Testis biopsies frequently demonstrate sperm in men with azoospermia and significantly elevated follicle-stimulating hormone levels. *J Urol*, 1997. 157: 144.
<https://www.ncbi.nlm.nih.gov/pubmed/8976237>
18. Deruyver, Y., et al. Outcome of microdissection TESE compared with conventional TESE in non-obstructive azoospermia: a systematic review. *Andrology*, 2014. 2: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/24193894>
19. Marconi, M., et al. Combined trifocal and microsurgical testicular sperm extraction is the best technique for testicular sperm retrieval in "low-chance" nonobstructive azoospermia. *Eur Urol*, 2012. 62: 713.
<https://www.ncbi.nlm.nih.gov/pubmed/22521095>

20. Schlegel, P.N. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. *Hum Reprod*, 1999. 14: 131.
<https://www.ncbi.nlm.nih.gov/pubmed/10374109>
21. Schwarzer, J.U., et al. No relationship between biopsy sites near the main testicular vessels or rete testis and successful sperm retrieval using conventional or microdissection biopsies in 220 non-obstructive azoospermic men. *Asian J Androl*, 2013. 15: 795.
<https://www.ncbi.nlm.nih.gov/pubmed/24013619>
22. Bernie, A.M., et al. Comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for nonobstructive azoospermia: a systematic review and meta-analysis. *Fertility and sterility*, 2015. 104: 1099.
<https://www.ncbi.nlm.nih.gov/pubmed/26263080>
23. Ben-Yosef, D., et al. Testicular sperm retrieval and cryopreservation prior to initiating ovarian stimulation as the first line approach in patients with non-obstructive azoospermia. *Hum Reprod*, 1999. 14: 1794.
<https://www.ncbi.nlm.nih.gov/pubmed/10402392>
24. Borges, E., Jr., et al. Testicular sperm results in elevated miscarriage rates compared to epididymal sperm in azoospermic patients. *Sao Paulo Med J*, 2002. 120: 122.
<https://www.ncbi.nlm.nih.gov/pubmed/12436160>
25. Ghanem, M., et al. Comparison of the outcome of intracytoplasmic sperm injection in obstructive and non-obstructive azoospermia in the first cycle: a report of case series and meta-analysis. *Int J Androl*, 2005. 28: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/15679616>
26. Gil Salom, M. [Spermatic recovery techniques for intracytoplasmic spermatozoid injection (ICSI) in male infertility]. *Arch Esp Urol*, 2004. 57: 1035.
<https://www.ncbi.nlm.nih.gov/pubmed/15624403>
27. Schwarzer, J.U., et al. Sperm retrieval procedures and intracytoplasmic spermatozoa injection with epididymal and testicular sperms. *Urol Int*, 2003. 70: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/12592040>
28. Colpi, G.M., et al. Is transrectal ultrasonography a reliable diagnostic approach in ejaculatory duct sub-obstruction? *Hum Reprod*, 1997. 12: 2186.
<https://www.ncbi.nlm.nih.gov/pubmed/9402280>
29. Vernaev, V., et al. Intracytoplasmic sperm injection with testicular spermatozoa is less successful in men with nonobstructive azoospermia than in men with obstructive azoospermia. *Fertil Steril*, 2003. 79: 529.
<https://www.ncbi.nlm.nih.gov/pubmed/12620435>
30. Vloeberghs, V., et al. How successful is TESE-ICSI in couples with non-obstructive azoospermia? *Hum Reprod*, 2015. 30: 1790.
<https://www.ncbi.nlm.nih.gov/pubmed/26082482>
31. Belva, F., et al. Neonatal outcome of 724 children born after ICSI using non-ejaculated sperm. *Hum Reprod*, 2011. 26: 1752.
<https://www.ncbi.nlm.nih.gov/pubmed/21511713>
32. Carrell, D.T. The clinical implementation of sperm chromosome aneuploidy testing: pitfalls and promises. *J Androl*, 2008. 29: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/17881765>
33. Johnson, M.D. Genetic risks of intracytoplasmic sperm injection in the treatment of male infertility: recommendations for genetic counseling and screening. *Fertil Steril*, 1998. 70: 397.
<https://www.ncbi.nlm.nih.gov/pubmed/9757865>
34. Clementini, E., et al. Prevalence of chromosomal abnormalities in 2078 infertile couples referred for assisted reproductive techniques. *Hum Reprod*, 2005. 20: 437.
<https://www.ncbi.nlm.nih.gov/pubmed/15567875>
35. Vincent, M.C., et al. Cytogenetic investigations of infertile men with low sperm counts: a 25-year experience. *J Androl*, 2002. 23: 18.
<https://www.ncbi.nlm.nih.gov/pubmed/11780918>
36. Dul, E.C., et al. The prevalence of chromosomal abnormalities in subgroups of infertile men. *Hum Reprod*, 2012. 27: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/22081244>
37. Davila Garza, S.A., et al. Reproductive outcomes in patients with male infertility because of Klinefelter's syndrome, Kartagener's syndrome, round-head sperm, dysplasia fibrous sheath, and 'stump' tail sperm: an updated literature review. *Curr Opin Obstet Gynecol*, 2013. 25: 229.
<https://www.ncbi.nlm.nih.gov/pubmed/23587797>

38. Wang, C., et al. Hormonal studies in Klinefelter's syndrome. *Clin Endocrinol (Oxf)*, 1975. 4: 399.
<https://www.ncbi.nlm.nih.gov/pubmed/1157343>
39. Staessen, C., et al. PGD in 47,XXY Klinefelter's syndrome patients. *Hum Reprod Update*, 2003. 9: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/12926526>
40. Chevret, E., et al. Increased incidence of hyperhaploid 24,XY spermatozoa detected by three-colour FISH in a 46,XY/47,XXY male. *Hum Genet*, 1996. 97: 171.
<https://www.ncbi.nlm.nih.gov/pubmed/8566948>
41. Martini, E., et al. Constitution of semen samples from XYY and XXY males as analysed by in-situ hybridization. *Hum Reprod*, 1996. 11: 1638.
<https://www.ncbi.nlm.nih.gov/pubmed/8921108>
42. Cozzi, J., et al. Achievement of meiosis in XXY germ cells: study of 543 sperm karyotypes from an XY/XXY mosaic patient. *Hum Genet*, 1994. 93: 32.
<https://www.ncbi.nlm.nih.gov/pubmed/8270252>
43. Estop, A.M., et al. Meiotic products of a Klinefelter 47,XXY male as determined by sperm fluorescence in-situ hybridization analysis. *Hum Reprod*, 1998. 13: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/9512242>
44. Foresta, C., et al. High incidence of sperm sex chromosomes aneuploidies in two patients with Klinefelter's syndrome. *J Clin Endocrinol Metab*, 1998. 83: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/9435442>
45. Guttenbach, M., et al. Segregation of sex chromosomes into sperm nuclei in a man with 47,XXY Klinefelter's karyotype: a FISH analysis. *Hum Genet*, 1997. 99: 474.
<https://www.ncbi.nlm.nih.gov/pubmed/9099836>
46. Aksglaede, L., et al. Testicular function and fertility in men with Klinefelter syndrome: a review. *Eur J Endocrinol*, 2013. 168: R67.
<https://www.ncbi.nlm.nih.gov/pubmed/23504510>
47. Gies, I., et al. Spermatogonial stem cell preservation in boys with Klinefelter syndrome: to bank or not to bank, that's the question. *Fertil Steril*, 2012. 98: 284.
<https://www.ncbi.nlm.nih.gov/pubmed/22608314>
48. Nguyen, M.H., et al. Balanced complex chromosome rearrangement in male infertility: case report and literature review. *Andrologia*, 2015. 47: 178.
<https://www.ncbi.nlm.nih.gov/pubmed/24612408>
49. Siffroi, J.P., et al. Assisted reproductive technology and complex chromosomal rearrangements: the limits of ICSI. *Mol Hum Reprod*, 1997. 3: 847.
<https://www.ncbi.nlm.nih.gov/pubmed/9395262>
50. Gianaroli, L., et al. Frequency of aneuploidy in sperm from patients with extremely severe male factor infertility. *Hum Reprod*, 2005. 20: 2140.
<https://www.ncbi.nlm.nih.gov/pubmed/15845594>
51. Pang, M.G., et al. The high incidence of meiotic errors increases with decreased sperm count in severe male factor infertilities. *Hum Reprod*, 2005. 20: 1688.
<https://www.ncbi.nlm.nih.gov/pubmed/15734753>
52. Tempest, H.G., et al. Cytogenetic risks in chromosomally normal infertile men. *Curr Opin Obstet Gynecol*, 2009. 21: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/19424064>
53. Baccetti, B., et al. Ultrastructural studies of spermatozoa from infertile males with Robertsonian translocations and 18, X, Y aneuploidies. *Hum Reprod*, 2005. 20: 2295.
<https://www.ncbi.nlm.nih.gov/pubmed/15878922>
54. Miyagawa, Y., et al. Outcome of gonadotropin therapy for male hypogonadotropic hypogonadism at university affiliated male infertility centers: a 30-year retrospective study. *J Urol*, 2005. 173: 2072.
<https://www.ncbi.nlm.nih.gov/pubmed/15879837>
55. Ferlin, A., et al. Male infertility and androgen receptor gene mutations: clinical features and identification of seven novel mutations. *Clin Endocrinol (Oxf)*, 2006. 65: 606.
<https://www.ncbi.nlm.nih.gov/pubmed/17054461>
56. Gottlieb, B., et al. Molecular pathology of the androgen receptor in male (in)fertility. *Reprod Biomed Online*, 2005. 10: 42.
<https://www.ncbi.nlm.nih.gov/pubmed/15705293>
57. Rajender, S., et al. Phenotypic heterogeneity of mutations in androgen receptor gene. *Asian J Androl*, 2007. 9: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/17334586>

58. Tincello, D.G., et al. Preliminary investigations on androgen receptor gene mutations in infertile men. *Mol Hum Reprod*, 1997. 3: 941.
<https://www.ncbi.nlm.nih.gov/pubmed/9433918>
59. Giwercman, A., et al. Preserved male fertility despite decreased androgen sensitivity caused by a mutation in the ligand-binding domain of the androgen receptor gene. *J Clin Endocrinol Metab*, 2000. 85: 2253.
<https://www.ncbi.nlm.nih.gov/pubmed/10852459>
60. Wang, P.J. X chromosomes, retrogenes and their role in male reproduction. *Trends Endocrinol Metab*, 2004. 15: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/15036254>
61. Nuti, F., et al. Gene polymorphisms/mutations relevant to abnormal spermatogenesis. *Reprod Biomed Online*, 2008. 16: 504.
<https://www.ncbi.nlm.nih.gov/pubmed/18413059>
62. Stouffs, K., et al. Male infertility and the involvement of the X chromosome. *Hum Reprod Update*, 2009. 15: 623.
<https://www.ncbi.nlm.nih.gov/pubmed/19515807>
63. Krausz, C., et al. High resolution X chromosome-specific array-CGH detects new CNVs in infertile males. *PLoS One*, 2012. 7: e44887.
<https://www.ncbi.nlm.nih.gov/pubmed/23056185>
64. Tuttelmann, F., et al. Copy number variants in patients with severe oligozoospermia and Sertoli-cell-only syndrome. *PLoS One*, 2011. 6: e19426.
<https://www.ncbi.nlm.nih.gov/pubmed/21559371>
65. Vogt, P.H., et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. *Hum Mol Genet*, 1996. 5: 933.
<https://www.ncbi.nlm.nih.gov/pubmed/8817327>
66. Krausz, C., et al. Y chromosome and male infertility: update, 2006. *Front Biosci*, 2006. 11: 3049.
<https://www.ncbi.nlm.nih.gov/pubmed/16720375>
67. Skaletsky, H., et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature*, 2003. 423: 825.
<https://www.ncbi.nlm.nih.gov/pubmed/12815422>
68. Tyler-Smith, C., et al. The will-o'-the-wisp of genetics--hunting for the azoospermia factor gene. *N Engl J Med*, 2009. 360: 925.
<https://www.ncbi.nlm.nih.gov/pubmed/19246366>
69. Krausz, C., et al. The Y chromosome and male fertility and infertility. *Int J Androl*, 2003. 26: 70.
<https://www.ncbi.nlm.nih.gov/pubmed/12641824>
70. Krausz, C., et al. EAA/EMQN best practice guidelines for molecular diagnosis of Y-chromosomal microdeletions: state-of-the-art 2013. *Andrology*, 2014. 2: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/24357628>
71. Stuppia, L., et al. A quarter of men with idiopathic oligo-azoospermia display chromosomal abnormalities and microdeletions of different types in interval 6 of Yq11. *Hum Genet*, 1998. 102: 566.
<https://www.ncbi.nlm.nih.gov/pubmed/9654206>
72. Le Bourhis, C., et al. Y chromosome microdeletions and germinal mosaicism in infertile males. *Mol Hum Reprod*, 2000. 6: 688.
<https://www.ncbi.nlm.nih.gov/pubmed/10908277>
73. Siffroi, J.P., et al. Sex chromosome mosaicism in males carrying Y chromosome long arm deletions. *Hum Reprod*, 2000. 15: 2559.
<https://www.ncbi.nlm.nih.gov/pubmed/11098026>
74. Patsalis, P.C., et al. Effects of transmission of Y chromosome AZFc deletions. *Lancet*, 2002. 360: 1222.
<https://www.ncbi.nlm.nih.gov/pubmed/12401251>
75. Repping, S., et al. Polymorphism for a 1.6-Mb deletion of the human Y chromosome persists through balance between recurrent mutation and haploid selection. *Nat Genet*, 2003. 35: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/14528305>
76. Giachini, C., et al. Partial AZFc deletions and duplications: clinical correlates in the Italian population. *Hum Genet*, 2008. 124: 399.
<https://www.ncbi.nlm.nih.gov/pubmed/18807255>
77. Navarro-Costa, P., et al. The AZFc region of the Y chromosome: at the crossroads between genetic diversity and male infertility. *Hum Reprod Update*, 2010. 16: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/20304777>

78. Stouffs, K., et al. What about gr/gr deletions and male infertility? Systematic review and meta-analysis. *Hum Reprod Update*, 2011. 17: 197.
<https://www.ncbi.nlm.nih.gov/pubmed/20959348>
79. Nathanson, K.L., et al. The Y deletion gr/gr and susceptibility to testicular germ cell tumor. *Am J Hum Genet*, 2005. 77: 1034.
<https://www.ncbi.nlm.nih.gov/pubmed/16380914>
80. Pavlovich, C.P., et al. Fertility options after vasectomy: a cost-effectiveness analysis. *Fertil Steril*, 1997. 67: 133.
<https://www.ncbi.nlm.nih.gov/pubmed/8986698>
81. Zhang, F., et al. Partial deletions are associated with an increased risk of complete deletion in AZFc: a new insight into the role of partial AZFc deletions in male infertility. *J Med Genet*, 2007. 44: 437.
<https://www.ncbi.nlm.nih.gov/pubmed/17412880>
82. Donat, R., et al. The incidence of cystic fibrosis gene mutations in patients with congenital bilateral absence of the vas deferens in Scotland. *Br J Urol*, 1997. 79: 74.
<https://www.ncbi.nlm.nih.gov/pubmed/9043501>
83. Chillon, M., et al. Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. *N Engl J Med*, 1995. 332: 1475.
<https://www.ncbi.nlm.nih.gov/pubmed/7739684>
84. De Braekeleer, M., et al. Mutations in the cystic fibrosis gene in men with congenital bilateral absence of the vas deferens. *Mol Hum Reprod*, 1996. 2: 669.
<https://www.ncbi.nlm.nih.gov/pubmed/9239681>
85. Krausz, C., et al. Genetic risk factors in male infertility. *Arch Androl*, 2007. 53: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/17612870>
86. Augarten, A., et al. Congenital bilateral absence of vas deferens in the absence of cystic fibrosis. *Lancet*, 1994. 344: 1473.
<https://www.ncbi.nlm.nih.gov/pubmed/7968122>
87. Drake, M.J., et al. Absent vas deferens and ipsilateral multicystic dysplastic kidney in a child. *Br J Urol*, 1996. 77: 756.
<https://www.ncbi.nlm.nih.gov/pubmed/8689131>
88. Tuttelmann, F., et al. Gene polymorphisms and male infertility--a meta-analysis and literature review. *Reprod Biomed Online*, 2007. 15: 643.
<https://www.ncbi.nlm.nih.gov/pubmed/18062861>
89. ESHRE Capri Workshop Group. Intracytoplasmic sperm injection (ICSI) in 2006: evidence and evolution. *Hum Reprod Update*, 2007. 13: 515.
<https://www.ncbi.nlm.nih.gov/pubmed/17630396>
90. Davies, M.J., et al. Reproductive technologies and the risk of birth defects. *N Engl J Med*, 2012. 366: 1803.
<https://www.ncbi.nlm.nih.gov/pubmed/22559061>
91. Van Steirteghem, A., et al. Follow-up of children born after ICSI. *Hum Reprod Update*, 2002. 8: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/12099626>
92. Zini, A., et al. Are tests of sperm DNA damage clinically useful? Pros and cons. *J Androl*, 2009. 30: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/19059901>
93. Hendry, W., Azoospermia and surgery for testicular obstruction. In: Hargreave TB (ed). *Male Infertility*, in Hargreave TB (ed). *Male Infertility*. 1997, Springer Verlag: Berlin.
http://link.springer.com/chapter/10.1007%2F978-1-4471-1029-3_17#page-1
94. Hendry, W.F., et al. Exploratory scrototomy in 168 azoospermic males. *Br J Urol*, 1983. 55: 785.
<https://www.ncbi.nlm.nih.gov/pubmed/6652453>
95. Jequier, A.M. Obstructive azoospermia: a study of 102 patients. *Clin Reprod Fertil*, 1985. 3: 21.
<https://www.ncbi.nlm.nih.gov/pubmed/3978535>
96. Oates, R.D., et al. The genetic basis of congenital bilateral absence of the vas deferens and cystic fibrosis. *J Androl*, 1994. 15: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/8188533>
97. Pierik, F.H., et al. Serum inhibin B as a marker of spermatogenesis. *J Clin Endocrinol Metab*, 1998. 83: 3110.
<https://www.ncbi.nlm.nih.gov/pubmed/9745412>
98. Handelsman, D.J., et al. Young's syndrome. Obstructive azoospermia and chronic sinopulmonary infections. *N Engl J Med*, 1984. 310: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/6689737>

99. Schoysman, R. Vaso-epididymostomy--a survey of techniques and results with considerations of delay of appearance of spermatozoa after surgery. *Acta Eur Fertil*, 1990. 21: 239.
<https://www.ncbi.nlm.nih.gov/pubmed/2132475>
100. Silber, S.J., et al. Microscopic vasectomy reversal 30 years later: a summary of 4010 cases by the same surgeon. *J Androl*, 2004. 25: 845.
<https://www.ncbi.nlm.nih.gov/pubmed/15477352>
101. Jarvi, K., et al. Adverse effects on vasoepididymostomy outcomes for men with concomitant abnormalities in the prostate and seminal vesicle. *J Urol*, 1998. 160: 1410.
<https://www.ncbi.nlm.nih.gov/pubmed/9751365>
102. Matthews, G.J., et al. Patency following microsurgical vasoepididymostomy and vasovasostomy: temporal considerations. *J Urol*, 1995. 154: 2070.
<https://www.ncbi.nlm.nih.gov/pubmed/7500460>
103. Borovikov, A., Treatment of large vasal defects. In: Goldstein M (ed). *Surgery of Male Infertility*. 1995, WB Saunders: Philadelphia.
104. Shin, D., et al. Herniorrhaphy with polypropylene mesh causing inguinal vasal obstruction: a preventable cause of obstructive azoospermia. *Ann Surg*, 2005. 241: 553.
<https://www.ncbi.nlm.nih.gov/pubmed/15798455>
105. Schlegel, P.N., et al. Urogenital anomalies in men with congenital absence of the vas deferens. *J Urol*, 1996. 155: 1644.
<https://www.ncbi.nlm.nih.gov/pubmed/8627844>
106. Elder, J.S., et al. Cyst of the ejaculatory duct/urogenital sinus. *J Urol*, 1984. 132: 768.
<https://www.ncbi.nlm.nih.gov/pubmed/6471229>
107. Schuhrke, T.D., et al. Prostatic utricle cysts (mullerian duct cysts). *J Urol*, 1978. 119: 765.
<https://www.ncbi.nlm.nih.gov/pubmed/26814>
108. Surya, B.V., et al. Cysts of the seminal vesicles: diagnosis and management. *Br J Urol*, 1988. 62: 491.
<https://www.ncbi.nlm.nih.gov/pubmed/3208033>
109. Schroeder-Printzen, I., et al. Surgical therapy in infertile men with ejaculatory duct obstruction: technique and outcome of a standardized surgical approach. *Hum Reprod*, 2000. 15: 1364.
<https://www.ncbi.nlm.nih.gov/pubmed/10831570>
110. Kuligowska, E., et al. Male infertility: role of transrectal US in diagnosis and management. *Radiology*, 1992. 185: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/1410338>
111. Colpi, G.M., et al. Functional voiding disturbances of the ampullo-vesicular seminal tract: a cause of male infertility. *Acta Eur Fertil*, 1987. 18: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/3125711>
112. Silber, S.J., et al. Pregnancy with sperm aspiration from the proximal head of the epididymis: a new treatment for congenital absence of the vas deferens. *Fertil Steril*, 1988. 50: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/3410105>
113. Esteves, S.C., et al. Sperm retrieval techniques for assisted reproduction. *Int Braz J Urol*, 2011. 37: 570.
<https://www.ncbi.nlm.nih.gov/pubmed/22099268>
114. Schroeder-Printzen, I., et al. Microsurgical epididymal sperm aspiration: aspirate analysis and straws available after cryopreservation in patients with non-reconstructable obstructive azoospermia. MESA/TESE Group Giessen. *Hum Reprod*, 2000. 15: 2531.
<https://www.ncbi.nlm.nih.gov/pubmed/11098022>
115. Van Peperstraten, A., et al. Techniques for surgical retrieval of sperm prior to ICSI for azoospermia. *Cochrane Database Syst Rev*, 2006: CD002807.
<https://www.ncbi.nlm.nih.gov/pubmed/16855991>
116. Peng, J., et al. Microsurgical vasoepididymostomy is an effective treatment for azoospermic patients with epididymal obstruction and prior failure to achieve pregnancy by sperm retrieval with intracytoplasmic sperm injection. *Human Reproduction*, 2014. 29 (1): 1.
<https://www.ncbi.nlm.nih.gov/pubmed/24218402>
117. Mangoli, V., et al. The outcome of ART in males with impaired spermatogenesis. *J Hum Reprod Sci*, 2008. 1: 73.
<https://www.ncbi.nlm.nih.gov/pubmed/19562049>
118. Kolettis, P.N., et al. Vasoepididymostomy for vasectomy reversal: a critical assessment in the era of intracytoplasmic sperm injection. *J Urol*, 1997. 158: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/9224325>

119. Ruiz-Romero, J., et al. A new device for microsurgical sperm aspiration. *Andrologia*, 1994. 26: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/8042769>
120. Fisch, H., et al. Management of ejaculatory duct obstruction: etiology, diagnosis, and treatment. *World J Urol*, 2006. 24: 604.
<https://www.ncbi.nlm.nih.gov/pubmed/17077974>
121. WHO, WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male. 2000, Cambridge University Press: Cambridge.
<http://www.who.int/reproductivehealth/publications/infertility/0521774748/en/>
122. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. *Fertil Steril*, 1992. 57: 1289.
<https://www.ncbi.nlm.nih.gov/pubmed/1601152>
123. Agarwal, A., et al. Efficacy of varicocelectomy in improving semen parameters: new meta-analytical approach. *Urology*, 2007. 70: 532.
<https://www.ncbi.nlm.nih.gov/pubmed/17905111>
124. Zini, A., et al. Are varicoceles associated with increased deoxyribonucleic acid fragmentation? *Fertil Steril*, 2011. 96: 1283.
<https://www.ncbi.nlm.nih.gov/pubmed/>
125. Baazeem, A., et al. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. *Eur Urol*, 2011. 60: 796.
<https://www.ncbi.nlm.nih.gov/pubmed/21733620>
126. Esteves, S.C., et al. Outcome of varicocele repair in men with nonobstructive azoospermia: Systematic review and meta-analysis. *Asian J Androl*, 2016. 18: 246.
<https://www.ncbi.nlm.nih.gov/pubmed/26680033>
127. Yamamoto, M., et al. Effect of varicocelectomy on sperm parameters and pregnancy rate in patients with subclinical varicocele: a randomized prospective controlled study. *J Urol*, 1996. 155: 1636.
<https://www.ncbi.nlm.nih.gov/pubmed/8627841>
128. Breznik, R., et al. Treatment of varicocele and male fertility. *Arch Androl*, 1993. 30: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/8498867>
129. Kroese, A.C., et al. Surgery or embolization for varicoceles in subfertile men. *Cochrane Database Syst Rev*, 2012. 10: CD000479.
<https://www.ncbi.nlm.nih.gov/pubmed/23076888>
130. Ding, H., et al. Open non-microsurgical, laparoscopic or open microsurgical varicocelectomy for male infertility: a meta-analysis of randomized controlled trials. *BJU Int*, 2012. 110: 1536.
<https://www.ncbi.nlm.nih.gov/pubmed/22642226>
131. Tauber, R., et al. Antegrade scrotal sclerotherapy for the treatment of varicocele: technique and late results. *J Urol*, 1994. 151: 386.
<https://www.ncbi.nlm.nih.gov/pubmed/8283530>
132. Sigmund, G., et al. Idiopathic varicoceles: feasibility of percutaneous sclerotherapy. *Radiology*, 1987. 164: 161.
<https://www.ncbi.nlm.nih.gov/pubmed/3588899>
133. Lenk, S., et al. Comparison of different methods of treating varicocele. *J Androl*, 1994. 15 Suppl: 34S.
<https://www.ncbi.nlm.nih.gov/pubmed/7721674>
134. Seyferth, W., et al. Percutaneous sclerotherapy of varicocele. *Radiology*, 1981. 139: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/7220877>
135. Ivanissevich, O. Left varicocele due to reflux; experience with 4,470 operative cases in forty-two years. *J Int Coll Surg*, 1960. 34: 742.
<https://www.ncbi.nlm.nih.gov/pubmed/13718224>
136. Palomo, A. Radical cure of varicocele by a new technique; preliminary report. *J Urol*, 1949. 61: 604.
<https://www.ncbi.nlm.nih.gov/pubmed/18114752>
137. Goldstein, M., et al. Microsurgical inguinal varicocelectomy with delivery of the testis: an artery and lymphatic sparing technique. *J Urol*, 1992. 148: 1808.
<https://www.ncbi.nlm.nih.gov/pubmed/1433614>
138. Jungwirth, A., et al. Clinical outcome of microsurgical subinguinal varicocelectomy in infertile men. *Andrologia*, 2001. 33: 71.
<https://www.ncbi.nlm.nih.gov/pubmed/11350369>
139. Miersch, W.D., et al. Laparoscopic varicocelectomy: indication, technique and surgical results. *Br J Urol*, 1995. 76: 636.
<https://www.ncbi.nlm.nih.gov/pubmed/8535687>

140. Tan, S.M., et al. Laparoscopic varicocelectomy: technique and results. *Br J Urol*, 1995. 75: 523.
<https://www.ncbi.nlm.nih.gov/pubmed/7788264>
141. Bianco, S.D., et al. The genetic and molecular basis of idiopathic hypogonadotropic hypogonadism. *Nat Rev Endocrinol*, 2009. 5: 569.
<https://www.ncbi.nlm.nih.gov/pubmed/19707180>
142. Krausz, C. Genetic aspects of male infertility. *European Urological Review*, 2009. 3.
http://link.springer.com/chapter/10.1007/978-3-540-48461-5_1
143. Dwyer, A.A., et al. Gonadotrophin replacement for induction of fertility in hypogonadal men. *Best Pract Res Clin Endocrinol Metab*, 2015. 29: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/25617175>
144. Schopohl, J., et al. Comparison of gonadotropin-releasing hormone and gonadotropin therapy in male patients with idiopathic hypothalamic hypogonadism. *Fertil Steril*, 1991. 56: 1143.
<https://www.ncbi.nlm.nih.gov/pubmed/1743335>
145. Andersson, A.M., et al. Impaired Leydig cell function in infertile men: a study of 357 idiopathic infertile men and 318 proven fertile controls. *J Clin Endocrinol Metab*, 2004. 89: 3161.
<https://www.ncbi.nlm.nih.gov/pubmed/15240588>
146. Lanfranco, F., et al. Klinefelter's syndrome. *Lancet*, 2004. 364: 273.
<https://www.ncbi.nlm.nih.gov/pubmed/15262106>
147. Manning, M., et al. Decrease in testosterone blood concentrations after testicular sperm extraction for intracytoplasmic sperm injection in azoospermic men. *Lancet*, 1998. 352: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/9800753>
148. Finkelstein, J., Androgens and bone metabolism. In: Nieschlag E, Behre HM (eds). *Testosterone: Action, Deficiency, Substitution*. 2nd edition, in *Testosterone: Action, Deficiency, Substitution*. 1998, Springer Verlag: Berlin. p. 187.
http://link.springer.com/chapter/10.1007%2F978-3-642-72185-4_6#page-1
149. Dohle, G., et al., Guidelines on Male Hypogonadism, in In: *EAU Guidelines*, edn. presented on the 27th EAU Annual Congress, Paris 2012. 2012.
<https://uroweb.org/guideline/male-hypogonadism/>
150. Berkowitz, G.S., et al. Prevalence and natural history of cryptorchidism. *Pediatrics*, 1993. 92: 44.
<https://www.ncbi.nlm.nih.gov/pubmed/8100060>
151. Skakkebaek, N.E., et al. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod*, 2001. 16: 972.
<https://www.ncbi.nlm.nih.gov/pubmed/11331648>
152. Gracia, J., et al. Clinical and anatomopathological study of 2000 cryptorchid testes. *Br J Urol*, 1995. 75: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/7613821>
153. Hadziselimovic, F., et al. Infertility in cryptorchidism is linked to the stage of germ cell development at orchidopexy. *Horm Res*, 2007. 68: 46.
<https://www.ncbi.nlm.nih.gov/pubmed/17356291>
154. Kolon, T.F., et al. Evaluation and treatment of cryptorchidism: AUA guideline. *Journal of Urology*, 2014. 192 (2): 337.
<https://www.ncbi.nlm.nih.gov/pubmed/24857650>
155. Tekgül, S., et al. EAU/ESPU Guidelines on Paediatric Urology. *EAU Guidelines* edn. presented at the 31st EAU Annual Congress, Munich 2016.
<https://uroweb.org/guideline/paediatric-urology/>
156. Yavetz, H., et al. Cryptorchidism: incidence and sperm quality in infertile men. *Andrologia*, 1992. 24: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/1356318>
157. Wilkerson, M.L., et al. Fertility potential: a comparison of intra-abdominal and intracanalicular testes by age groups in children. *Horm Res*, 2001. 55: 18.
<https://www.ncbi.nlm.nih.gov/pubmed/11423737>
158. Giwercman, A., et al. Initiation of sperm production after bilateral orchiopexy: clinical and biological implications. *J Urol*, 2000. 163: 1255.
<https://www.ncbi.nlm.nih.gov/pubmed/10737515>
159. Giwercman, A., et al. Prevalence of carcinoma *in situ* and other histopathological abnormalities in testes of men with a history of cryptorchidism. *J Urol*, 1989. 142: 998.
<https://www.ncbi.nlm.nih.gov/pubmed/2571738>
160. Pettersson, A., et al. Age at surgery for undescended testis and risk of testicular cancer. *N Engl J Med*, 2007. 356: 1835.
<https://www.ncbi.nlm.nih.gov/pubmed/17476009>

161. Bloom, D.A. Two-step orchiopepy with pelviscopic clip ligation of the spermatic vessels. *J Urol*, 1991. 145: 1030.
<https://www.ncbi.nlm.nih.gov/pubmed/1673160>
162. Jones, P.F. Approaches to orchidopexy. *Br J Urol*, 1995. 75: 693.
<https://www.ncbi.nlm.nih.gov/pubmed/>
163. Heidenreich, A., et al. Contralateral testicular biopsy procedure in patients with unilateral testis cancer: is it indicated? *Semin Urol Oncol*, 2002. 20: 234.
<https://www.ncbi.nlm.nih.gov/pubmed/12489055>
164. Pierik, F.H., et al. The advantages of standardized evaluation of male infertility. *Int J Androl*, 2000. 23: 340.
<https://www.ncbi.nlm.nih.gov/pubmed/11114979>
165. Foresta, C., et al. Suppression of the high endogenous levels of plasma FSH in infertile men are associated with improved Sertoli cell function as reflected by elevated levels of plasma inhibin B. *Hum Reprod*, 2004. 19: 1431.
<https://www.ncbi.nlm.nih.gov/pubmed/15117900>
166. Chua, M.E., et al. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. *Andrology*, 2013. 1: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/23970453>
167. Santi, D., et al. FSH treatment of male idiopathic infertility improves pregnancy rate: A meta-analysis. *Endocr Connect*, 2015. 4: R46.
<https://www.ncbi.nlm.nih.gov/pubmed/26113521>
168. Imamovic Kumalic, S., et al. Review of clinical trials on effects of oral antioxidants on basic semen and other parameters in idiopathic oligoasthenoteratozoospermia. [Review]. *BioMed Research International*, 2014. 426951.
<https://www.ncbi.nlm.nih.gov/pubmed/24800224>
169. Showell, M.G., et al. Antioxidants for male subfertility. *The Cochrane database of systematic reviews*, 2014. 12: CD007411.
<https://www.ncbi.nlm.nih.gov/pubmed/25504418>
170. Ross, C., et al. A systematic review of the effect of oral antioxidants on male infertility. *Reprod Biomed Online*, 2010. 20: 711.
<https://www.ncbi.nlm.nih.gov/pubmed/20378409>
171. WHO. Reproductive Health Strategy. Reproductive Health Research World Health Organisation, Geneva. Adopted at the 57th World Health Assembly. 2004.
http://who.int/reproductivehealth/publications/general/RHR_04_8/en/
172. Handelsman, D.J., et al., Tradional methods. In: Schill W, Comhaire F, Hargreave T (eds). *Andrology for the Clinician*, in *Andrology for the Clinician*. 2006, Springer Verlag: Berlin.
173. Matthiesson, K.L., et al. Male hormonal contraception: concept proven, product in sight? *Hum Reprod Update*, 2006. 12: 463.
<https://www.ncbi.nlm.nih.gov/pubmed/16597629>
174. Kogan, P., et al. Male contraception: History and development. *Urologic Clinics of North America*, 2014. 41 (1): 145.
<https://www.ncbi.nlm.nih.gov/pubmed/24286773>
175. Handelsman, D., et al., Hormonal male contraception. In: Schill W, Comhaire F, Hargreave T (eds). *Andrology for the Clinician*, in *Andrology for the Clinician*. 2006, Springer Verlag: Berlin.
176. Holden, C.A., et al. Sexual activity, fertility and contraceptive use in middle-aged and older men: Men in Australia, Telephone Survey (MATeS). *Hum Reprod*, 2005. 20: 3429.
<https://www.ncbi.nlm.nih.gov/pubmed/16172145>
177. Cook, L.A., et al. Scalpel versus no-scalpel incision for vasectomy [Systematic Review]. *Cochrane Database Syst Rev*, 2014. 3: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/24683021>
178. Li, S.Q., et al. The no-scalpel vasectomy. *J Urol*, 1991. 145: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/1988727>
179. Barone, M.A., et al. Effectiveness of vasectomy using cautery. *BMC Urol*, 2004. 4: 10.
<https://www.ncbi.nlm.nih.gov/pubmed/15260885>
180. Rubio C., et al. Improvement of clinical outcome in severe male factor infertility with embryo selection based on array-CGH: A randomized controlled trial. *Fertility and sterility*, 2014. 102: e24.
[http://www.fertstert.org/article/S0015-0282\(14\)00718-3/abstract](http://www.fertstert.org/article/S0015-0282(14)00718-3/abstract)
181. Sharlip, I.D., et al. Vasectomy: AUA guideline. *J Urol*, 2012. 188: 2482.
<https://www.ncbi.nlm.nih.gov/pubmed/23098786>

182. Schwingl, P.J., et al. Safety and effectiveness of vasectomy. *Fertil Steril*, 2000. 73: 923.
<https://www.ncbi.nlm.nih.gov/pubmed/10785217>
183. Bernal-Delgado, E., et al. The association between vasectomy and prostate cancer: a systematic review of the literature. *Fertil Steril*, 1998. 70: 191.
<https://www.ncbi.nlm.nih.gov/pubmed/9696205>
184. Christiansen, C.G., et al. Testicular pain following vasectomy: a review of postvasectomy pain syndrome. *J Androl*, 2003. 24: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/12721203>
185. Nirapathongporn, A., et al. No-scalpel vasectomy at the King's birthday vasectomy festival. *Lancet*, 1990. 335: 894.
<https://www.ncbi.nlm.nih.gov/pubmed/1969992>
186. Verhulst, A.P., et al. Paternity after bilateral vasectomy. *BJU Int*, 1999. 83: 280.
<https://www.ncbi.nlm.nih.gov/pubmed/10233494>
187. Korthorst, R.A., et al. Clearance after vasectomy with a single semen sample containing < than 100 000 immotile sperm/mL: analysis of 1073 patients. *BJU Int*, 2010. 105: 1572.
<https://www.ncbi.nlm.nih.gov/pubmed/20002679>
188. Sokal, D., et al. A comparison of vas occlusion techniques: cautery more effective than ligation and excision with fascial interposition. *BMC Urol*, 2004. 4: 12.
<https://www.ncbi.nlm.nih.gov/pubmed/15509302>
189. Sokal, D., et al. Vasectomy by ligation and excision, with or without fascial interposition: a randomized controlled trial [ISRCTN77781689]. *BMC Med*, 2004. 2: 6.
<https://www.ncbi.nlm.nih.gov/pubmed/15056388>
190. Schroeder-Printzen, I., et al. Vasovasostomy. *Urol Int*, 2003. 70: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/12592037>
191. Belker, A.M., et al. Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J Urol*, 1991. 145: 505.
<https://www.ncbi.nlm.nih.gov/pubmed/1997700>
192. Chan, P.T., et al. Prospective analysis of outcomes after microsurgical intussusception vasoepididymostomy. *BJU Int*, 2005. 96: 598.
<https://www.ncbi.nlm.nih.gov/pubmed/16104917>
193. Cook, L.A., et al. Vasectomy techniques for male sterilization: systematic Cochrane review of randomized controlled trials and controlled clinical trials. *Hum Reprod*, 2004. 19: 2431.
<https://www.ncbi.nlm.nih.gov/pubmed/15496598>
194. Heidenreich, A., et al. Microsurgical vasovasostomy versus microsurgical epididymal sperm aspiration/testicular extraction of sperm combined with intracytoplasmic sperm injection. A cost-benefit analysis. *Eur Urol*, 2000. 37: 609.
<https://www.ncbi.nlm.nih.gov/pubmed/10765102>
195. Purvis, K., et al. Infection in the male reproductive tract. Impact, diagnosis and treatment in relation to male infertility. *Int J Androl*, 1993. 16: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/8468091>
196. Weidner, W., et al. Relevance of male accessory gland infection for subsequent fertility with special focus on prostatitis. *Hum Reprod Update*, 1999. 5: 421.
<https://www.ncbi.nlm.nih.gov/pubmed/10582781>
197. Liversedge, N.H., et al. Antibiotic treatment based on seminal cultures from asymptomatic male partners in in-vitro fertilization is unnecessary and may be detrimental. *Hum Reprod*, 1996. 11: 1227.
<https://www.ncbi.nlm.nih.gov/pubmed/8671429>
198. Taylor-Robinson, D. Evaluation and comparison of tests to diagnose *Chlamydia trachomatis* genital infections. *Hum Reprod*, 1997. 12: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/>
199. Weidner, W., et al. Ureaplasma infections of the male urogenital tract, in particular prostatitis, and semen quality. *Urol Int*, 1985. 40: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/>
200. Taylor-Robinson, D. Infections due to species of *Mycoplasma* and *Ureaplasma*: an update. *Clin Infect Dis*, 1996. 23: 671.
<https://www.ncbi.nlm.nih.gov/pubmed/8909826>
201. Aitken, R.J., et al. Seminal leukocytes: passengers, terrorists or good samaritans? *Hum Reprod*, 1995. 10: 1736.
<https://www.ncbi.nlm.nih.gov/pubmed/8582971>

202. Trum, J.W., et al. Value of detecting leukocytospermia in the diagnosis of genital tract infection in subfertile men. *Fertil Steril*, 1998. 70: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/9696227>
203. Krieger, J.N., et al. Seminal fluid findings in men with nonbacterial prostatitis and prostatodynia. *J Androl*, 1996. 17: 310.
<https://www.ncbi.nlm.nih.gov/pubmed/8792222>
204. Weidner, W., et al. Semen parameters in men with and without proven chronic prostatitis. *Arch Androl*, 1991. 26: 173.
<https://www.ncbi.nlm.nih.gov/pubmed/1872650>
205. Christiansen, E., et al. Sperm quality in men with chronic abacterial prostatovesiculitis verified by rectal ultrasonography. *Urology*, 1991. 38: 545.
<https://www.ncbi.nlm.nih.gov/pubmed/1746084>
206. Giamarellou, H., et al. Infertility and chronic prostatitis. *Andrologia*, 1984. 16: 417.
<https://www.ncbi.nlm.nih.gov/pubmed/6496959>
207. Leib, Z., et al. Reduced semen quality caused by chronic abacterial prostatitis: an enigma or reality? *Fertil Steril*, 1994. 61: 1109.
<https://www.ncbi.nlm.nih.gov/pubmed/8194626>
208. Wolff, H. The biologic significance of white blood cells in semen. *Fertil Steril*, 1995. 63: 1143.
<https://www.ncbi.nlm.nih.gov/pubmed/7750580>
209. Wolff, H., et al. Impact of clinically silent inflammation on male genital tract organs as reflected by biochemical markers in semen. *J Androl*, 1991. 12: 331.
<https://www.ncbi.nlm.nih.gov/pubmed/1765569>
210. Dousset, B., et al. Seminal cytokine concentrations (IL-1beta, IL-2, IL-6, sR IL-2, sR IL-6), semen parameters and blood hormonal status in male infertility. *Hum Reprod*, 1997. 12: 1476.
<https://www.ncbi.nlm.nih.gov/pubmed/9262280>
211. Huleihel, M., et al. Distinct expression levels of cytokines and soluble cytokine receptors in seminal plasma of fertile and infertile men. *Fertil Steril*, 1996. 66: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/8752625>
212. Shimonovitz, S., et al. High concentration of soluble interleukin-2 receptors in ejaculate with low sperm motility. *Hum Reprod*, 1994. 9: 653.
<https://www.ncbi.nlm.nih.gov/pubmed/8046017>
213. Zalata, A., et al. Evaluation of beta-endorphin and interleukin-6 in seminal plasma of patients with certain andrological diseases. *Hum Reprod*, 1995. 10: 3161.
<https://www.ncbi.nlm.nih.gov/pubmed/8822435>
214. Alexander, R.B., et al. Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis/chronic pelvic pain syndrome. *Urology*, 1998. 52: 744.
<https://www.ncbi.nlm.nih.gov/pubmed/9801092>
215. Comhaire, F., et al. Diagnosis of accessory gland infection and its possible role in male infertility. *Int J Androl*, 1980. 3: 32.
<https://www.ncbi.nlm.nih.gov/pubmed/7409893>
216. Depuydt, C.E., et al. The relation between reactive oxygen species and cytokines in andrological patients with or without male accessory gland infection. *J Androl*, 1996. 17: 699.
<https://www.ncbi.nlm.nih.gov/pubmed/9016401>
217. Schaeffer, A.J. Clinical practice. Chronic prostatitis and the chronic pelvic pain syndrome. *N Engl J Med*, 2006. 355: 1690.
<https://www.ncbi.nlm.nih.gov/pubmed/17050893>
218. Wagenlehner, F.M., et al. Chronic bacterial prostatitis (NIH type II): diagnosis, therapy and influence on the fertility status. *Andrologia*, 2008. 40: 100.
<https://www.ncbi.nlm.nih.gov/pubmed/18336459>
219. Weidner, W., et al. Therapy in male accessory gland infection--what is fact, what is fiction? *Andrologia*, 1998. 30 Suppl 1: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/9629448>
220. Comhaire, F.H., et al. The effect of doxycycline in infertile couples with male accessory gland infection: a double blind prospective study. *Int J Androl*, 1986. 9: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/3539821>
221. Berger, R., Epididymitis. In: Holmes KK, Mardh PA, Sparling PF et al. (eds). *Sexually Transmitted Diseases*, in *Sexually Transmitted Diseases*. 1984, McGraw-Hill: New York.
222. Berger, R.E., et al. Etiology, manifestations and therapy of acute epididymitis: prospective study of 50 cases. *J Urol*, 1979. 121: 750.
<https://www.ncbi.nlm.nih.gov/pubmed/379366>

223. Weidner, W., et al. Acute nongonococcal epididymitis. Aetiological and therapeutic aspects. *Drugs*, 1987. 34 Suppl 1: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/3481311>
224. National guideline for the management of epididymo-orchitis. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). *Sex Transm Infect*, 1999. 75 Suppl 1: S51.
<https://www.ncbi.nlm.nih.gov/pubmed/10616385>
225. Weidner, W., et al., Orchitis. In: Knobil E, Neill JD (eds) *Encyclopedia of Reproduction*, in *Encyclopedia of Reproduction*. 1999, Academic Press: San Diego.
226. Robinson, A.J., et al. Acute epididymitis: why patient and consort must be investigated. *Br J Urol*, 1990. 66: 642.
<https://www.ncbi.nlm.nih.gov/pubmed/2265337>
227. Skakkebaek, N.E. Carcinoma *in situ* of the testis: frequency and relationship to invasive germ cell tumours in infertile men. *Histopathology*, 1978. 2: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/27442>
228. von der Maase, H., et al. Carcinoma *in situ* of contralateral testis in patients with testicular germ cell cancer: study of 27 cases in 500 patients. *Br Med J (Clin Res Ed)*, 1986. 293: 1398.
<https://www.ncbi.nlm.nih.gov/pubmed/3026550>
229. Jacobsen, R., et al. Risk of testicular cancer in men with abnormal semen characteristics: cohort study. *BMJ*, 2000. 321: 789.
<https://www.ncbi.nlm.nih.gov/pubmed/11009515>
230. van Casteren, N.J., et al. Testicular microlithiasis and carcinoma *in situ* overview and proposed clinical guideline. *Int J Androl*, 2009. 32: 279.
<https://www.ncbi.nlm.nih.gov/pubmed/19207616>
231. Huyghe, E., et al. Increasing incidence of testicular cancer worldwide: a review. *J Urol*, 2003. 170: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/12796635>
232. Giwercman, A., et al. Carcinoma *in situ* of the undescended testis. *Semin Urol*, 1988. 6: 110.
<https://www.ncbi.nlm.nih.gov/pubmed/2903524>
233. Petersen, P.M., et al. Semen quality and reproductive hormones before orchiectomy in men with testicular cancer. *J Clin Oncol*, 1999. 17: 941.
<https://www.ncbi.nlm.nih.gov/pubmed/10071288>
234. Eberhard, J., et al. Impact of therapy and androgen receptor polymorphism on sperm concentration in men treated for testicular germ cell cancer: a longitudinal study. *Hum Reprod*, 2004. 19: 1418.
<https://www.ncbi.nlm.nih.gov/pubmed/15105386>
235. Willemse, P.H., et al. Altered Leydig cell function in patients with testicular cancer: evidence for bilateral testicular defect. *Acta Endocrinol (Copenh)*, 1983. 102: 616.
<https://www.ncbi.nlm.nih.gov/pubmed/6133401>
236. Nord, C., et al. Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. *Eur Urol*, 2003. 44: 322.
<https://www.ncbi.nlm.nih.gov/pubmed/12932930>
237. Eberhard, J., et al. Sexual function in men treated for testicular cancer. *J Sex Med*, 2009. 6: 1979.
<https://www.ncbi.nlm.nih.gov/pubmed/19453896>
238. Schrader, M., et al. "Onco-tese": testicular sperm extraction in azoospermic cancer patients before chemotherapy-new guidelines? *Urology*, 2003. 61: 421.
<https://www.ncbi.nlm.nih.gov/pubmed/12597960>
239. Peterson, A.C., et al. The prevalence of testicular microlithiasis in an asymptomatic population of men 18 to 35 years old. *J Urol*, 2001. 166: 2061.
<https://www.ncbi.nlm.nih.gov/pubmed/11696707>
240. von Eckardstein, S., et al. Sonographic testicular microlithiasis as an indicator of premalignant conditions in normal and infertile men. *J Androl*, 2001. 22: 818.
<https://www.ncbi.nlm.nih.gov/pubmed/11545295>
241. Richenberg, J., et al. Testicular microlithiasis imaging and follow-up: guidelines of the ESUR scrotal imaging subcommittee. *Eur Radiol*, 2015. 25: 323.
<https://www.ncbi.nlm.nih.gov/pubmed/25316054>
242. Pierik, F.H., et al. Is routine scrotal ultrasound advantageous in infertile men? *J Urol*, 1999. 162: 1618.
<https://www.ncbi.nlm.nih.gov/pubmed/10524881>
243. Derogee, M., et al. Testicular microlithiasis, a premalignant condition: prevalence, histopathologic findings, and relation to testicular tumor. *Urology*, 2001. 57: 1133.
<https://www.ncbi.nlm.nih.gov/pubmed/11377326>

244. Giwercman, A., et al. Prevalence of carcinoma *in situ* and other histopathological abnormalities in testes from 399 men who died suddenly and unexpectedly. *J Urol*, 1991. 145: 77.
<https://www.ncbi.nlm.nih.gov/pubmed/2571738>
245. Miller, F.N., et al. Does testicular microlithiasis matter? A review. *Clin Radiol*, 2002. 57: 883.
<https://www.ncbi.nlm.nih.gov/pubmed/12413911>
246. de Gouveia Brazao, C.A., et al. Bilateral testicular microlithiasis predicts the presence of the precursor of testicular germ cell tumors in subfertile men. *J Urol*, 2004. 171: 158.
<https://www.ncbi.nlm.nih.gov/pubmed/14665866>
247. Buvat, J., Glossaire. [Disruptions in ejaculation] In: Buvat J, Jouannet P (eds). [Ejaculation and its Disruptions.], in *Ejaculation and its Disruptions*. 1984, SIMEP: Lyon-Villeurbanne.
248. Wang, R., et al., Ejaculatory dysfunction. In: Comhaire FH (ed). *Male Infertility: Clinical Investigation. Cause, Evaluation and Treatment*, in *Male Infertility: Clinical Investigation. Cause, Evaluation and Treatment*. 1996, Chapman Hall: London.
249. Pryor, J., Erectile and ejaculatory problems in infertility. In: Hargreave TB (ed). *Male Infertility*, in *Male Infertility*. 1997, Springer Verlag: Berlin.
250. Yachia, D. Our experience with penile deformations: incidence, operative techniques, and results. *J Androl*, 1994. 15 Suppl: 63S.
<https://www.ncbi.nlm.nih.gov/pubmed/7721682>
251. Rudkin, L., et al. Strategies for managing sexual dysfunction induced by antidepressant medication. *Cochrane Database Syst Rev*, 2004: CD003382.
<https://www.ncbi.nlm.nih.gov/pubmed/15495050>
252. Abdel-Hamid, I.A., et al. Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. *Int J Impot Res*, 2001. 13: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/11313839>
253. Demyttenaere, K., et al. Painful ejaculation and urinary hesitancy in association with antidepressant therapy: relief with tamsulosin. *Eur Neuropsychopharmacol*, 2002. 12: 337.
<https://www.ncbi.nlm.nih.gov/pubmed/12126873>
254. McMahon, C.G., et al. Oral agents for the treatment of premature ejaculation: review of efficacy and safety in the context of the recent International Society for Sexual Medicine criteria for lifelong premature ejaculation. *J Sex Med*, 2011. 8: 2707.
<https://www.ncbi.nlm.nih.gov/pubmed/21771283>
255. Crich, J.P., et al. Infertility in men with retrograde ejaculation: the action of urine on sperm motility, and a simple method for achieving antegrade ejaculation. *Fertil Steril*, 1978. 30: 572.
<https://www.ncbi.nlm.nih.gov/pubmed/720646>
256. Gilja, I., et al. Retrograde ejaculation and loss of emission: possibilities of conservative treatment. *Eur Urol*, 1994. 25: 226.
<https://www.ncbi.nlm.nih.gov/pubmed/8200405>
257. Mehta, A., et al. Management of the dry ejaculate: A systematic review of aspermia and retrograde ejaculation. *Fertility and Sterility*, 2015. 104: 1074.
<https://www.ncbi.nlm.nih.gov/pubmed/26432530>
258. Schill, W.B. Pregnancy after brompheniramine treatment of a diabetic with incomplete emission failure. *Arch Androl*, 1990. 25: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/2389987>
259. Hendry, W.F. Disorders of ejaculation: congenital, acquired and functional. *Br J Urol*, 1998. 82: 331.
<https://www.ncbi.nlm.nih.gov/pubmed/9772867>
260. Brindley, G.S. Reflex ejaculation under vibratory stimulation in paraplegic men. *Paraplegia*, 1981. 19: 299.
<https://www.ncbi.nlm.nih.gov/pubmed/7279433>
261. Elliott, S., et al., Treatment of anejaculation. In: Colpi GM, Balerna M (eds). *Treating Male Infertility: New Possibilities*, in *Treating Male Infertility: New Possibilities*. 1994, Karger AG: Basel.
262. Waldinger, M.D. The neurobiological approach to premature ejaculation. *J Urol*, 2002. 168: 2359.
<https://www.ncbi.nlm.nih.gov/pubmed/12441918>
263. Jankowicz, E., et al. [Idiopathic autonomic neuropathy (pandysautonomia)]. *Neurol Neurochir Pol*, 2001. 35: 439.
<https://www.ncbi.nlm.nih.gov/pubmed/11732267>
264. Maurer, C.A., et al. Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery. *Br J Surg*, 2001. 88: 1501.
<https://www.ncbi.nlm.nih.gov/pubmed/11683749>
265. Tournaye, H., et al. Fertility preservation in men with cancer. *Lancet*, 2014. 384: 1295.
<https://www.ncbi.nlm.nih.gov/pubmed/25283570>

266. Askari, H.A., et al. Effect of natural antioxidants tocopherol and ascorbic acids in maintenance of sperm activity during freeze-thaw process. *Arch Androl*, 1994. 33: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/7979804>
267. Chohan, K.R., et al. Evaluation of chromatin integrity in human sperm using acridine orange staining with different fixatives and after cryopreservation. *Andrologia*, 2004. 36: 321.
<https://www.ncbi.nlm.nih.gov/pubmed/15458552>
268. Desrosiers, P., et al. Membranous and structural damage that occur during cryopreservation of human sperm may be time-related events. *Fertil Steril*, 2006. 85: 1744.
<https://www.ncbi.nlm.nih.gov/pubmed/16643911>
269. Donnelly, E.T., et al. Cryopreservation of human semen and prepared sperm: effects on motility parameters and DNA integrity. *Fertil Steril*, 2001. 76: 892.
<https://www.ncbi.nlm.nih.gov/pubmed/11704107>
270. Agarwal, A., et al. Oxidative stress, DNA damage and apoptosis in male infertility: a clinical approach. *BJU Int*, 2005. 95: 503.
<https://www.ncbi.nlm.nih.gov/pubmed/15705068>
271. Smith, K.D., et al. Survival of spermatozoa in a human sperm bank. Effects of long-term storage in liquid nitrogen. *JAMA*, 1973. 223: 774.
<https://www.ncbi.nlm.nih.gov/pubmed/4739258>
272. Grischenko, V.I., et al. Cryopreservation of human sperm using rapid cooling rates. *Cryo Letters*, 2003. 24: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/12819827>
273. Sherman, J.K., et al. Observations on preservation of human spermatozoa at low temperatures. *Proc Soc Exp Biol Med*, 1953. 82: 686.
<https://www.ncbi.nlm.nih.gov/pubmed/13055973>
274. Sawada, Y., et al. Motility and respiration of human spermatozoa after cooling to various low temperatures. *Fertil Steril*, 1967. 18: 775.
<https://www.ncbi.nlm.nih.gov/pubmed/6073928>
275. Bahadur, G., et al. Semen quality and cryopreservation in adolescent cancer patients. *Hum Reprod*, 2002. 17: 3157.
<https://www.ncbi.nlm.nih.gov/pubmed/12456617>
276. Hallak, J., et al. Investigation of fertilizing capacity of cryopreserved spermatozoa from patients with cancer. *J Urol*, 1998. 159: 1217.
<https://www.ncbi.nlm.nih.gov/pubmed/9507838>
277. Clarke, G.N. Sperm cryopreservation: is there a significant risk of cross-contamination? *Hum Reprod*, 1999. 14: 2941.
<https://www.ncbi.nlm.nih.gov/pubmed/10601075>
278. O'Connell, M., et al. The effects of cryopreservation on sperm morphology, motility and mitochondrial function. *Hum Reprod*, 2002. 17: 704.
<https://www.ncbi.nlm.nih.gov/pubmed/11870124>
279. Watson, P.F. Recent developments and concepts in the cryopreservation of spermatozoa and the assessment of their post-thawing function. *Reprod Fertil Dev*, 1995. 7: 871.
<https://www.ncbi.nlm.nih.gov/pubmed/8711221>
280. Woolley, D.M., et al. Ultrastructural injury to human spermatozoa after freezing and thawing. *J Reprod Fertil*, 1978. 53: 389.
<https://www.ncbi.nlm.nih.gov/pubmed/567693>

7. CONFLICT OF INTEREST

All members of the EAU Chronic Pelvic Pain Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website <http://www.uroweb.org/guidelines/>. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Male Hypogonadism

G.R. Dohle (Chair), S. Arver, C. Bettocchi,
T.H. Jones, S. Kliesch

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1. INTRODUCTION

1.1 Aim

Androgens play a crucial role in the development and maintenance of male reproductive and sexual functions, body composition, erythropoiesis, muscle and bone health, and cognitive functions. Low levels of circulating androgens in utero can cause disturbances in male sexual development, resulting in congenital abnormalities of the male reproductive tract, such as testicular dysfunction, testicular maldescensus and hypospadias. Later in life, this may result in reduced male fertility, sexual dysfunction, decreased muscle formation and bone mineralisation, disturbances of fat metabolism and cognitive dysfunction and may contribute to the development of testicular tumours. Testosterone levels decrease slightly as a process of ageing; risks factors for developing adult onset hypogonadism are: obesity, chronic diseases and a poor general health. Symptomatic hypogonadal patients may benefit from testosterone treatment. This document presents the European Association of Urology (EAU) Guidelines on the diagnosis and treatment of male hypogonadism, with the aim to provide practical recommendations on how to deal with primary and secondary forms of hypogonadism, ageing-related decline in testosterone in men, as well as the treatment of testosterone deficiencies.

It must be emphasised that clinical guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not and should not purport to be a legal standard of care.

1.2 Publication history

These Guidelines are a series of revisions of the first edition of the EAU Guidelines on Male Hypogonadism published in 2012.

1.3 Available Publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the Male Hypogonadism Guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of EAU guidelines articles as well as translations produced by national urological associations: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Panel composition

The EAU Male Hypogonadism Panel consists of a multidisciplinary group of experts, including urologists specialising in andrology and endocrinologists.

2. METHODS

2.1 Introduction

References used in this text are assessed according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR) according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence [1]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://www.uroweb.org/guideline/>. A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

The recommendations provided in these guidelines are based on a systematic literature search and review performed by the panel members in 2016. MedLine, Embase and Cochrane databases were searched to identify original articles and review articles. The controlled vocabulary of the Medical Subject Headings (MeSH) database was used alongside a 'free-text' protocol, combining 'male hypogonadism' with the terms 'diagnosis', 'epidemiology', 'investigations', 'treatment', 'testosterone', 'androgens' and 'hypogonadism'.

For the 2017 update, a scoping search was performed, covering all areas of the guideline and the search terms 'hypogonadism', 'eugonadal or hypogonadism or hypogonadal or gonadal', and 'low or lower testosterone', starting from 2011 with a cut-off date of April 2016. Embase, Medline and the Cochrane Central Register

of Controlled Trials databases were searched, with a limitation to reviews, meta-analyses or meta-analysis of randomised controlled trials. A total of 2,252 unique records were identified, retrieved and screened for relevance, of which 51 publications were selected for inclusion. A detail search strategy is available online: <http://www.uroweb.org/guideline/male-hypogonadism/>.

2.2 Review

This document was subject to peer review prior to publication in 2015.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2018 update of the Male Hypogonadism Guidelines. Ongoing systematic reviews are:-

- What are the risks of major cardiovascular events from testosterone replacement therapy (TRT)? [2].
- What are the benefits and harms of testosterone treatment for male sexual dysfunction? [3].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Definition: male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (QoL) [4]. A diagnosis of male hypogonadism must comprise both persistent clinical symptoms and biochemical evidence of testosterone deficiency.

Androgen deficiency increases slightly with age also in healthy men [5, 6]. In middle-aged men, the incidence of biochemical hypogonadism varies from 2.1-12.8% [7]. The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 varies from 2.1-5.7% [6, 7]. Hypogonadism is more prevalent in older men, in men with obesity, those with co-morbidities, and in men with a poor health status.

3.1.1 Role of testosterone for male reproductive health

Androgens, which are produced by the testis and by the adrenal glands, play a pivotal role in male reproductive and sexual function. Androgens are crucial for the development of male reproductive organs, such as the epididymis, vas deferens, seminal vesicle, prostate and penis. In addition, androgens are needed for puberty, male fertility, male sexual function, muscle formation, body composition, bone mineralisation, fat metabolism, and cognitive functions [8].

3.2 Physiology

Male sexual development starts between the 7th and 12th week of gestation. The undifferentiated gonads develop into a foetal testis through expression of multiple genes, including the sex-determining region of the Y chromosome (SRY gene complex) and the SOX genes [9]. The foetal testis produces three hormones: testosterone, insulin-like peptide 3 (INSL3) and anti-Müllerian hormone (AMH). Testosterone is needed for the stabilisation of the Wolffian ducts, resulting in formation of the epididymis, vas deferens and seminal vesicle. Anti-Müllerian hormone activity results in regression of the Müllerian ducts (Figure 1). INSL3, AMH and testosterone regulate testicular descent.

Under the influence of intratesticular testosterone, the number of gonocytes per tubule increases threefold during the foetal period [10]. In addition, testosterone is needed for development of the prostate, penis and scrotum. However, in these organs testosterone is converted into the more potent metabolite 5 α -dihydrotestosterone (DHT) by the enzyme 5 α -reductase. Testosterone and DHT are required for penile growth, both activating the androgen receptor [11].

Intratesticular testosterone is needed to maintain the spermatogenic process and to inhibit germ cell apoptosis [12]. The seminiferous tubules of the testes are exposed to concentrations of testosterone 25-100 times greater than circulating levels. Suppression of gonadotropins (e.g. through excessive testosterone abuse) results in a reduced number of spermatozoa in the ejaculate and hypospermatogenesis [13]. Complete inhibition of intratesticular testosterone results in full cessation of meiosis up to the level of round spermatids [14, 15]. Testosterone does not appear to act directly on the germ cells, but functions through the Sertoli cells by expression of the androgen receptor (AR) and influencing the seminiferous tubular microenvironment [15].

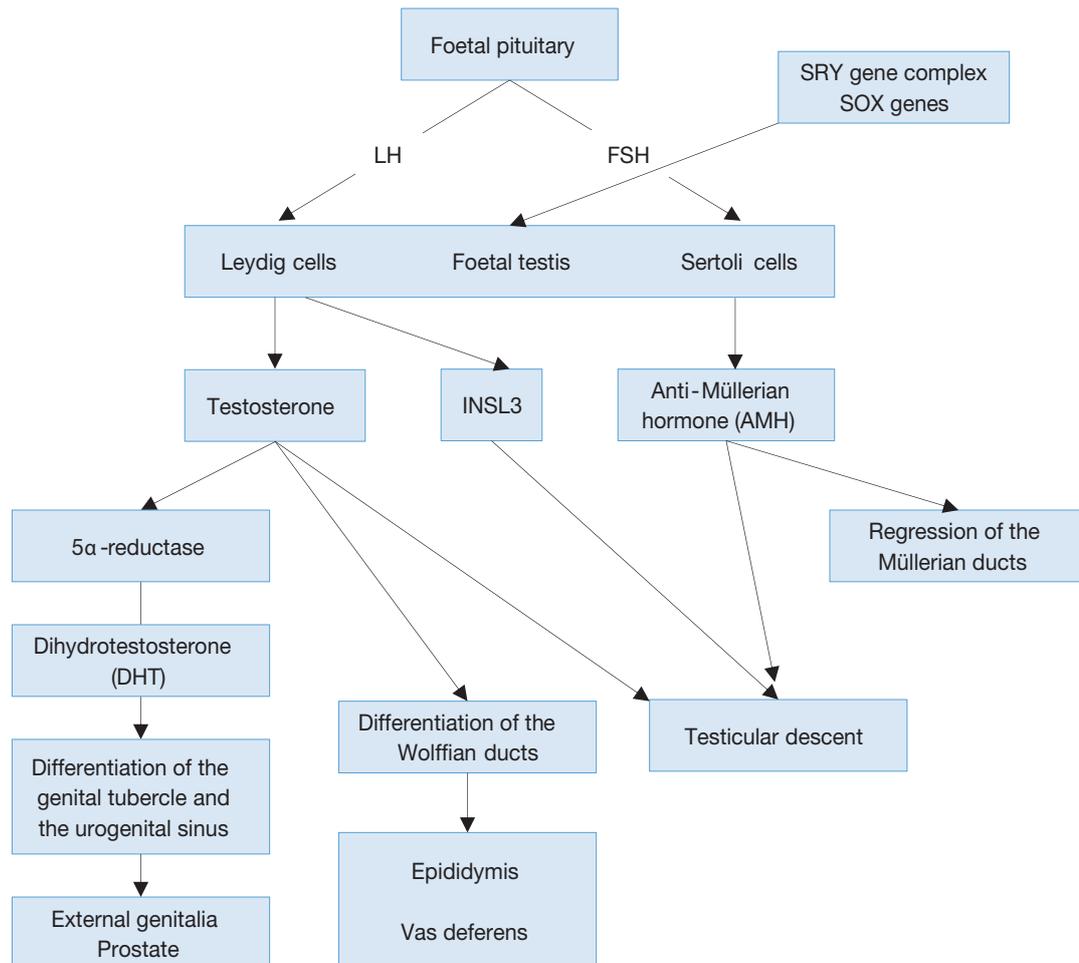
Testosterone can also be metabolised into oestradiol by aromatase, present in fat tissue, the prostate, the testes and bone. Oestradiol is also essential for bone mineralisation in men [16]. The production of testosterone is controlled in the foetus by placental chorion gonadotropin (hCG) and after birth by luteinising hormone (LH) from the pituitary gland. Immediately after birth, serum testosterone levels reach adult concentrations over several months (mini puberty). Thereafter and until puberty, testosterone levels are low, thus preventing male virilisation. Puberty starts with the production of gonadotropins, initiated by gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus and results in testosterone production, male sexual characteristics and spermatogenesis [17]. Figure 1 shows the development of the male reproductive system.

3.2.1 *The androgen receptor*

Testosterone exerts its action through the androgen receptor (AR), located in the cytoplasm and nucleus of target cells. During the foetal period, testosterone increases the number of ARs by increasing the number of cells with the AR and by increasing the number of ARs in each individual cell [11, 16]. The AR gene is located on the X chromosome (Xq 11-12): defects and mutations in the AR gene can result in male sexual maldevelopment, which may cause testicular feminisation or low virilisation (i.e. disorder of sexual development (DSD)). Less severe mutations in the AR gene may cause mild forms of androgen resistance and male infertility [18]. In exon 1 of the gene, the transactivation domain consists of a trinucleotide tract (cytosine-adenine-guanine (CAG) repeats) of variable length. Androgen sensitivity may be influenced by the length of the CAG repeats in exon 1 of the AR gene [18]. Shorter repeats have been associated with an increased risk for prostate disease, and longer repeats with reduced androgen action in several tissues [19]. CAG repeat number may influence androgenic phenotypical effects, even in case of normal testosterone levels [20].

Summary of evidence

Testosterone is essential for normal male development.
--

Figure 1: Development of the male reproductive system

FSH = follicle-stimulating hormone; LH = luteinising hormone; SRY = sex determining region of the Y chromosome; INSL3= insulin-like peptide 3.

3.3 Aetiology

Hypogonadism results from testicular failure, or is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis (Figure 2).

Male hypogonadism can be classified in accordance with disturbances at the level of:

- the testes (primary hypogonadism);
- the hypothalamus and pituitary (secondary hypogonadism);
- the hypothalamus/pituitary and gonads (common in adult-onset hypogonadism);
- androgen target organs (androgen insensitivity/resistance).

3.4 Classification

3.4.1 Male hypogonadism of testicular origin (primary hypogonadism)

Primary testicular failure is the most frequent cause of hypogonadism and results in low testosterone levels, impairment of spermatogenesis and elevated gonadotropins (high LH and FSH). The most common clinical forms of primary hypogonadism are Klinefelter syndrome and testicular tumours.

- Klinefelter syndrome affects 0.2% of the male population. It is the most frequent form of male hypogonadism and the most common numerical chromosomal aberration, with 47,XXY in 90% of cases [21]. It arises due to non-disjunction during paternal or maternal meiotic division of germ cells [22].
- Testicular tumours are the most frequent type of cancer in young males after puberty. Risk factors are contralateral germ cell cancer, maldescended testes, gonadal dysgenesis, infertility, testicular atrophy and familial germ cell cancer. Twenty-five per cent of men with testicular tumours develop testosterone deficiency after treatment [23-25].

The main reasons for primary hypogonadism are summarised in Table 1.

3.4.2 **Male hypogonadism of hypothalamic-hypopituitary origin (secondary hypogonadism)**

Central defects of the hypothalamus or pituitary cause secondary testicular failure. Identifying secondary hypogonadism is of clinical importance, as it can be a consequence of pituitary pathology (including prolactinomas) and can cause infertility, which can be restored by hormonal stimulation in most patients with secondary hypogonadism.

The most relevant forms of secondary hypogonadism are:

- *Hyperprolactinemia* (HP), caused by prolactin-secreting pituitary adenomas (prolactinomas) (microprolactinomas < 10 mm in diameter vs. macroprolactinomas) or drug-induced (by dopamine antagonist effects of substances such as phenothiazine, imipramine, risperidone and metoclopramide); additional causes may be chronic renal failure or hypothyroidism. Testosterone levels may however be normal despite the presence of a prolactinoma [26].
- *Isolated* (formerly termed idiopathic) or congenital hypogonadotropic hypogonadism (IHH, CHH).
- *Kallmann's syndrome* (hypogonadotropic hypogonadism with anosmia, genetically determined, prevalence one in 10,000 males).

These disorders are characterised by disturbed hypothalamic secretion (low LH and FSH) or low levels of gonadotropin-releasing hormone (GnRH). An inborn error of migration and homing of GnRH-secreting neurons results in Kallmann's syndrome [27, 28]. The most important symptom is the constitutional delay of puberty: it is the most common cause of delayed puberty (pubertas tarda) [29]. Other rare forms of secondary hypogonadism are listed in Table 2.

3.4.3 **Male hypogonadism due to mixed dysfunction of hypothalamus/pituitary and gonads (Adult-onset hypogonadism)**

Combined primary and secondary testicular failure results in low testosterone levels and variable gonadotropin levels. Gonadotropin levels depend predominantly on primary or secondary failure. What has also been labelled as late-onset hypogonadism and age-related hypogonadism is comprised of these two types of hypogonadism [30-32].

3.4.4 **Male hypogonadism due to defects of androgen target organs**

These forms are primarily rare defects and will not be further discussed in detail in these guidelines. There are AR defects with complete, partial and minimal androgen insensitivity syndrome; Reifenstein syndrome; bulbospinal muscular atrophy (Kennedy disease); as well as 5 α -reductase deficiency (for a review, see Nieschlag *et al.* 2010) [33].

The classification of hypogonadism has therapeutic implications. In patients with secondary hypogonadism, hormonal stimulation with hCG and FSH or alternatively pulsatile GnRH treatment can restore fertility in most cases [34, 35]. Detailed evaluation may, for example, detect pituitary tumours, systemic disease, or testicular tumours. Combined forms of primary and secondary hypogonadism can be observed in ageing, mostly obese men, with a concomitant age-related decline in testosterone levels resulting from defects in testicular as well as hypothalamic-pituitary function.

Table 1: Forms of primary hypogonadism

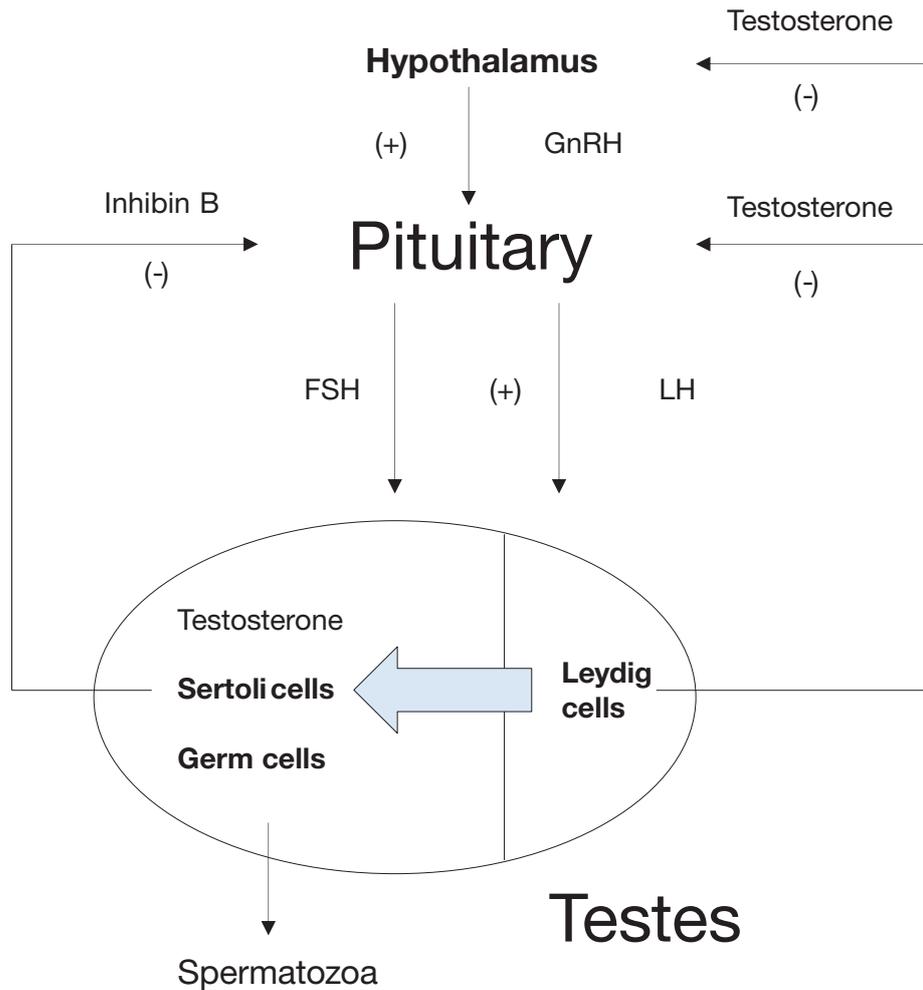
Disease	Causes of deficiency
Maldescended or ectopic testes	Failure of testicular descent, maldevelopment of the testis
Klinefelter syndrome 47,XXY	Sex-chromosomal non-disjunction in germ cells
Testicular cancer	Testicular maldevelopment
Orchitis	Viral or unspecific orchitis
Acquired anorchia	Trauma, tumour, torsion, inflammation, iatrogenic, surgical removal
Secondary testicular dysfunction	Medication, drugs, toxins, systemic diseases, varicocele
(Idiopathic) testicular atrophy/testicular dysgenesis	Male infertility (idiopathic or specific causes)
Congenital anorchia (bilateral in 1 in 20,000 males, unilateral 4 times as often)	Intrauterine torsion is the most probable cause
46,XY disorders of sexual development (DSD) (formerly male pseudohermaphroditism)	Disturbed testosterone synthesis due to enzymatic defects of steroid biosynthesis (17,20- hydroxylase defect, 17 β -hydroxysteroid dehydrogenase defect)
Gonadal dysgenesis (synonym 'streak gonads')	XY gonadal dysgenesis can be caused by mutations in different genes
46,XX male syndrome (prevalence of 1 in 10,000-20,000)	Males with presence of genetic information from the Y chromosome after translocation of a DNA segment of the Y to the X chromosome during paternal meiosis
Noonan syndrome (prevalence of 1 in 1,000 to 1 in 5,000)	Short stature, congenital heart diseases, cryptorchidism
Inactivating LH receptor mutations, Leydig cell hypoplasia (prevalence of 1 in 1,000,000 to 1 in 20,000)	Leydig cells are unable to develop due to the mutation [36]

Table 2: Forms of secondary hypogonadism

Disease	Causes of deficiency
Hyperprolactinemia	Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced
Isolated hypogonadotropic hypogonadism (IHH) (formerly termed idiopathic hypogonadotrophic hypogonadism)	Specific (or unknown) mutations affecting GnRH synthesis or action
Kallmann's syndrome (hypogonadotropic hypogonadism with anosmia, prevalence 1 in 10,000)	GnRH deficiency and anosmia, genetically determined
Secondary GnRH deficiency	Medication, drugs, toxins, systemic diseases
Hypopituitarism	Radiotherapy, trauma, infections, haemochromatosis and vascular insufficiency or congenital
Pituitary adenomas	Hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases to the pituitary or pituitary stalk
Prader-Willi syndrome (PWS) (formerly Prader-Labhart-Willi syndrome, prevalence 1 in 10,000 individuals)	Congenital disturbance of GnRH secretion
Congenital adrenal hypoplasia with hypogonadotropic hypogonadism (prevalence 1 in 12,500 individuals)	X-chromosomal recessive disease, in the majority of patients caused by mutations in the DAX1 gene
Pasqualini syndrome	Isolated LH deficiency

Recommendation	LE	GR
Differentiate the two forms of hypogonadism (primary and secondary hypogonadism) by determining luteinising hormone and follicle-stimulating hormone levels, as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.	1b	B

Figure 2: The hypothalamic-pituitary-testes axis



FSH = follicle-stimulating hormone; GnRH = Gonadotropin-releasing hormone; LH = luteinising hormone.

4. DIAGNOSTIC EVALUATION

Hypogonadism is diagnosed on the basis of persistent signs and symptoms related to androgen deficiency and assessment of consistently low testosterone levels (on at least two occasions) with a reliable method [7, 37-40]. It should be noted that over-time there is a substantial portion of men who recover from secondary hypogonadism, prompting the importance of re-evaluation if testosterone therapy has been instituted in men without defined hypothalamic or pituitary disease [41].

4.1 Clinical symptoms and laboratory testing

Low levels of circulating androgens may be associated with signs and symptoms (Table 3) [7, 42, 43]

Table 3: Clinical symptoms and signs suggestive for androgen deficiency

Clinical symptoms and signs suggestive for androgen deficiency:
Reduced testis volume
Male-factor infertility
Decreased body hair
Gynaecomastia
Decrease in lean body mass and muscle strength
Visceral obesity
Metabolic syndrome
Insulin resistance and type 2 diabetes mellitus
Decrease in bone mineral density (osteoporosis) with low trauma fractures
Mild anaemia
Sexual symptoms:
Reduced sexual desire and sexual activity
Erectile dysfunction
Fewer and diminished nocturnal erections
Cognitive and psychovegetative symptoms:
Hot flushes
Changes in mood, fatigue and anger
Sleep disturbances
Depression
Diminished cognitive function

The most prevalent symptoms of male hypogonadism in ageing men are reduced sexual desire and sexual activity, erectile dysfunction, loss of vigour and changes in mood [7, 43]. Other factors found associated with low testosterone are obesity and a poor general health status [7]. Signs and symptoms of androgen deficiency vary depending on age of onset, duration and the severity of the deficiency. Reference ranges for the lower normal level of testosterone (2.5%) have been compiled from three large community-based samples, suggesting a cut-off of 12.1 nmol/L for total serum testosterone and 243 pmol/L for free testosterone, to distinguish between normal levels and levels possibly associated with deficiency [44]. Symptoms suggesting the presence of hypogonadism [7, 43] are summarised in Table 3. It should, however, be noted that these symptoms are also found in men with normal testosterone levels and may have causes other than androgen deficiency.

In men aged 40-79 years, the threshold for total testosterone was 8 nmol/L for decreased frequency of sexual thoughts, 8.5 nmol/L for erectile dysfunction, 11 nmol/L for decreased frequency of morning erections and 13 nmol/L for diminished vigour [45, 46]. The strongest predictor for hypogonadism in this age group was three sexual symptoms (decreased sexual thoughts, weakened morning erections, erectile dysfunction) and either a total testosterone level of < 8 nmol/L or serum testosterone in the range of 8-11 nmol/L and free testosterone < 220 pmol/L. These data are based on serum samples taken in the morning, when mean levels are highest and most reproducible in younger men [47].

Laboratory testing of testosterone should reflect on the diurnal variation of testosterone. In most cases two morning (7.00 to 11.00) samples are sufficient, but should trigger further evaluation if the difference is > 20% [48]. Both immunoassay and mass spectrometry based assays can produce reliable results, as long as they are well-validated. Evaluation should be based on reference ranges for normal men provided by the laboratory measuring the samples.

In cases with discrepancy between testosterone levels and symptoms, free testosterone (FT) levels should be analysed. For determination of FT levels, the calculation of FT with the help of the sex hormone binding globulin (SHBG) is recommended.

Hypogonadism may be more subtle and not always evident by low testosterone levels. For example, men with primary testicular damage often have normal testosterone levels but high LH. This could be considered a sub-clinical or compensated form of hypogonadism. The clinical consequences of an isolated elevation of LH is not clear yet, but potentially, these men may become hypogonadal in the future.

To differentiate between primary and secondary forms of hypogonadism and to clarify hypogonadism in adult men, determination of LH serum levels is required. Both LH and testosterone serum levels should be analysed twice within 30 days, preferably in a fasting state [49].

4.2 History-taking and questionnaires

Symptoms of hypogonadism are listed in Table 3 and 4 and should be addressed during history-taking. Early onset of hypogonadism causes a lack of or minimal pubertal development, lack of development of secondary sex characteristics, possibly eunuchoid body proportions and a high-pitched voice. These signs and symptoms strongly suggest secondary hypogonadism. Adult-onset hypogonadism is characterised by sexual dysfunction, obesity and loss of vigour. Published questionnaires are unreliable, have low specificity and they are not effective for case-finding [50-53]. It is important to assess and exclude systemic illnesses, signs of malnutrition and malabsorption, as well as ongoing acute disease. Pharmacological treatments with corticosteroids, abuse of drugs such as marijuana, opiates and alcohol and previous treatment or use of testosterone and abuse of anabolic steroids should also be included in history-taking [54, 55].

4.3 Physical examination

Assessment of body mass index (BMI), the waist-hip ratio (or sagittal abdominal diameter), body hair, male pattern hair loss, presence of gynecomastia, testicular size (measured with an orchidometer or ultrasound [US]) and examination of the penis as well as a digital rectal examination (DRE) of the prostate should be included.

4.4 Summary of evidence and recommendations for the diagnostic evaluation

Summary of evidence
The diagnosis of male hypogonadism is based on signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.

Recommendations	LE	GR
Restrict the diagnosis of testosterone deficiency to men with persistent symptoms suggesting hypogonadism (Tables 3 and 4).	3	C
Measure testosterone in the morning before 11.00 hours, preferably in the fasting state.	2	A
Repeat total testosterone on at least two occasions with a reliable method. In addition, measure the free testosterone level in men with: <ul style="list-style-type: none"> - Total testosterone levels close to the lower normal range (8-12 nmol/L), to strengthen the laboratory assessment. - Suspected or known abnormal sex hormone-binding globulin (SHBG) levels. 	1	A
Assess testosterone in men with a disease or treatment in which testosterone deficiency is common and in whom treatment may be indicated. This includes men with: <ul style="list-style-type: none"> - Sexual dysfunction. - Type 2 diabetes. - Metabolic syndrome. - Obesity. - Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region. - Treatment with medications that cause suppression of testosterone levels - e.g. corticosteroids and opiates. - Moderate to severe chronic obstructive lung disease. - Infertility. - Osteoporosis or low-trauma fractures. - HIV infection with sarcopenia. 	2	B
Analyse LH serum levels to differentiate between primary and secondary forms of hypogonadism.	2	A

4.5 Clinical consequences of hypogonadism

The clinical consequences of hypogonadism are determined by the age of onset and the severity of hypogonadism.

4.5.1 Prenatal androgen deficiency

During the first fourteen weeks of gestation, the presence of testosterone is crucial for normal virilisation of the external male genitalia. Androgen deficiency or androgen resistance due to deficient AR or LH receptor function during this stage of life may result in abnormal genital development, ranging from hypospadias to

female external genitalia with intra-abdominal testis. Frequently, patients with disorders of sexual development are diagnosed at an early age because of clearly abnormal external genitalia. However, patients at both ends of the phenotypic spectrum may go unnoticed in childhood and are diagnosed during puberty because of delayed pubertal development.

4.5.2 **Prepubertal onset of androgen deficiency**

At the start of puberty, rising gonadotropin levels result in increasing testicular volume and the activation of spermatogenesis and testosterone secretion. During puberty, rising testosterone levels result in the development of male secondary sex characteristics, comprising deepening of the voice, development of terminal body hair, stimulation of hair growth in sex-specific regions, facial hair, increasing penile size, increase in muscle mass and bone size and mass, growth spurt induction and eventually closing of the epiphyses.

In addition, testosterone has explicit psychosexual effects, including increased libido. Delayed puberty is defined as an absence of testicular enlargement at the age of fourteen [56]. As this is a 'statistical' definition, based on reference ranges for the onset of puberty in the normal population, delayed puberty does not necessarily indicate the presence of a disease. In cases of severe androgen deficiency, the clinical picture of prepubertal onset hypogonadism is evident (Table 4) and diagnosis and treatment are fairly straightforward. The major challenge in younger individuals with presumed isolated (congenital) hypogonadotrophic hypogonadism is to differentiate the condition from a constitutional delay in puberty and to determine when to start androgen treatment. In milder cases of androgen deficiency, as seen in patients with Klinefelter syndrome, pubertal development can be normal, incomplete or delayed, resulting in a more subtle phenotypic picture. In these patients, several clues may lead to a diagnosis of hypogonadism. These include: small testes, (a history of) cryptorchidism, gynaecomastia, sparse body hair, eunuchoid habitus, low bone mass and sub-fertility [57].

Table 4: Signs and symptoms suggesting prepubertal-onset hypogonadism

Delayed puberty
Small testes
Cryptorchidism
Gynaecomastia
High-pitched voice
Unclosed epiphyses
Linear growth into adulthood
Eunuchoid habitus
Sparse body hair/facial hair
Infertility
Low bone mass
Sarcopenia
Reduced sexual desire/activity

4.5.3 **Adult-onset hypogonadism**

Adult-onset hypogonadism is defined as testosterone deficiency, usually associated with clinical symptoms or signs in a person who has had normal pubertal development and, as a result, developed normal male secondary sex characteristics.

Depending on the underlying cause of hypogonadism, the decline in gonadal function may be gradual and partial. The resulting clinical picture may be variable, and the signs and symptoms may be obscured by the physiological phenotypic variation. Symptoms that have been associated with adult-onset hypogonadism are summarised in Table 3. Most of these symptoms have a multi-factorial aetiology, are reminiscent of normal ageing and can also be found in men with completely normal testosterone levels [5]. As a result, signs and symptoms of adult-onset hypogonadism may be non-specific, and confirmation of a clinical suspicion by hormonal testing is mandatory. For many of the symptoms mentioned above, the probability of their presence increases with lower plasma testosterone levels. Most studies indicate a threshold level below which the prevalence of symptoms starts to increase [43, 58]. This threshold level is near the lower level of the normal range for plasma testosterone levels in young men, but there appears to be a wide variation between individuals and, even within one individual, the threshold level may be different for different target organs. Androgen receptor activity may also contribute to this variance [59, 60].

4.5.4 Hypogonadism in Type 2 Diabetes

There is a high prevalence of hypogonadism in men with type 2 diabetes mellitus [61-63]. The commonest symptom and main indication for treatment is that of sexual dysfunction. Erectile dysfunction has been reported in up to 70% of men with diabetes but may be caused by different or combined aetiologies (vasculopathy, neuropathy, medications, psychological factors) as well as hypogonadism in approximately 30%. Testosterone therapy alone may be insufficient and a combination with PDE5 inhibitors may be necessary. Testosterone deficiency is also associated with a failure of PDE5 inhibitor therapy [64]. Randomised controlled trials of at least six months duration testosterone treatment therapy (TRT) have reported significant improvement in sexual desire, but not erectile function [65-67] in men with type 2 diabetes, although one study did not find a benefit on sexual desire [68].

Testosterone deficiency is associated with an adverse cardiovascular risk profile in men with type 2 diabetes and TRT can improve insulin resistance and glycaemic control in some studies, reduce percentage body fat, and waist circumference and lower total and LDL-cholesterol, lipoprotein (a), and a small fall in HDL-cholesterol may occur. There is some evidence that it may reduce mortality [65, 69, 70]. These benefits, however, are not currently stand alone indications for TRT in type 2 diabetes and require further research but, could be considered as potential added benefits when used in conjunction when subjects are treated for sexual dysfunction.

4.5.4.1 Recommendations for screening men with adult-onset hypogonadism

Recommendations	LE	GR
Screen for testosterone deficiency only in adult men with consistent and multiple signs and symptoms listed in Table 3.	3	C
Young men with testicular dysfunction and men older than 50 years of age with low testosterone should additionally be screened for osteoporosis.	2	B

5. DISEASE MANAGEMENT

5.1 Indications and contraindications for treatment

Testosterone treatment aims to restore testosterone levels to the physiological range in men with consistently low levels of serum testosterone and associated symptoms of androgen deficiency. The aim of testosterone treatment is to restore physiological androgen dependent functions and to improve QoL, e.g. sense of well-being, sexual function, muscle strength and bone mineral density. Table 5 highlights the main indications for testosterone treatment. Table 6 lists the main contraindications against testosterone treatment.

Table 5: Main indications for testosterone treatment

Delayed puberty (constitutional or congenital forms (HH, Kallmann's syndrome))
Klinefelter syndrome with hypogonadism
Sexual dysfunction and low testosterone
Low bone mass in hypogonadism
Adult men with low testosterone and consistent and preferably multiple signs and symptoms of hypogonadism following unsuccessful treatment of obesity and comorbidities (listed in Table 3)
Hypopituitarism
Testicular dysfunctions and hypogonadism
Type 2 diabetes mellitus with hypogonadism

Table 6: Contraindications against testosterone treatment

Locally advanced or metastatic prostate cancer
Male breast cancer
Men with an active desire to have children
Haematocrit > 0.54
Severe chronic cardiac failure/New York Heart Association Class IV

5.2 Benefits of treatment

In congenital hypogonadotropic hypogonadism, treatment is usually indicated. In these patients hormonal stimulation with hCG and FSH or alternatively pulsatile GnRH treatment can induce puberty, restore fertility in most cases and normalise bone mineralisation [35, 71, 72]. If active desire to have children is not the focus of treatment after puberty induction, life-long testosterone substitution is recommended [73].

In adult-onset hypogonadism testosterone treatment may improve symptoms, but many hypogonadal men are sick and/or obese, and weight reduction, lifestyle modification and good treatment of comorbidities are more important than just testosterone treatment [74a, 74b].

Testosterone treatment may present several benefits regarding body composition, metabolic control, psychological and sexual parameters. Observational trials show a correlation between restored physiological testosterone levels, muscle mass and strength measured as leg press strength and quadriceps muscle volume [42, 75-77]. Low testosterone levels are common in men with chronic renal failure on haemodialysis and there is also a worsening of prognosis associated to lower testosterone levels. There is however, a lack of interventions studies evaluating eventual benefits of testosterone therapy in this group of men [78]. Similar positive results are shown in meta-analysis designed to address the value of the role of exogenous testosterone in bone mineral density: it is evident how testosterone therapy improves mineral density at the lumbar spine producing a reduction in bone resorption markers. Available trials failed to demonstrate a similar effect at the femoral neck. At present though, bone mineral density seems to remain a surrogate marker of bone health and there are no RCTs detailing actual bone fracture risk [76, 79-81]. Improvement in bone mineral density and bone structure in men with Klinefelter syndrome has also been reported [82]. Body composition is influenced by testosterone therapy in hypogonadal men, with a consequent decrease of fat mass and an increase in lean body mass [76, 83]. Men with hypogonadism are at an increased risk of having osteoporosis and osteopenia. Young men with testicular dysfunction and men older than 50 years of age with low testosterone should additionally be screened for osteoporosis [84].

Several studies based on testosterone undecanoate, demonstrate a significant reduction in trunk and waist fat with an evident decrease in waist size [85-87]. In the same trials, testosterone undecanoate administration showed an improvement in body weight, body mass index and lipid profile after three months of therapy [85].

A strong correlation between decreased testosterone levels and increased cardiovascular mortality has been reported in meta-analyses and retrospective studies showing that total-testosterone and free-testosterone in the normal range are related moreover to reduced all-cause mortality [88-94]. It is suggested that low testosterone is a biomarker for a poor health condition and as such is a marker for increased risk of cardiovascular disease [95]. Of interest is also the observation that testosterone treatment (transdermal) over a three year period compared to placebo did not cause any change in dynamics of atherosclerotic plaque development in the intima media of the carotids [96].

Sexual dysfunction and testosterone treatment

Sexual dysfunction symptoms are the most predictive determinant sign of potential male hypogonadism: 23 to 36% of men with sexual dysfunction are hypogonadal [97]. Testosterone therapy was shown to moderately increase sexual function in hypogonadal men [98]. In a large RCT, testosterone therapy resulted in a significant improvement of sexual arousal, interest and drive [99]. Two RCTs have reported that testosterone therapy has a benefit on sexual function in men with type 2 diabetes [65, 100]. In a recent meta-analyses of RCTs on testosterone therapy and sexual function, testosterone showed to have a positive influence on sexual function but only in clearly hypogonadal men ($T < 8$ nmol/L) [66]. Improvement of sexual symptoms will largely depend on the aetiology of the dysfunction: testosterone therapy in men with normal testosterone levels is not very effective, but testosterone therapy may help improve response to PDE5 inhibitors in hypogonadal men [101], although a recent meta analyses of studies with daily PDE5 inhibitors in men with low testosterone showed that PDE5 inhibitors were equally effective in men with low testosterone as in men with normal testosterone [102]. The advantage of the use of PDE5 inhibitors for erectile dysfunction is that these drugs are usually very effective and work fast. In contrast, testosterone treatment for erectile dysfunction may take up to several months to become effective. The use of a PDE5 inhibitor may also increase serum testosterone levels [103].

In a small RCT, testosterone therapy did not improve cognitive functions but had a positive effect on verbal memory and depressive symptoms [104]. Significant improvement of depressive symptoms in men treated with testosterone undecanoate were reported in a recent randomised trial [67]. Meta-analysis of data from randomised placebo-controlled trials has shown a significant positive impact of testosterone on mood [105].

In a recent review it is highlighted that QoL and physical function appears to improve in frail men with low testosterone, when treated with testosterone [46].

Summary of evidence	LE
Testosterone treatment may improve symptoms, but many hypogonadal men have a chronic illness and are obese. Weight reduction, lifestyle modification and good treatment of comorbidities can increase testosterone and reduce associated risks for diabetes and cardiovascular diseases.	2
Testosterone treatment can improve body composition, bone mineralisation, signs of the metabolic syndrome, male sexual problems, diabetes regulations, memory and depressive symptoms.	3
A reduction in BMI and waist size, improved glycaemic control and lipid profile are observed in hypogonadal men receiving testosterone treatment.	2a

Recommendations	LE	GR
Improve lifestyle, reduce weight in case of obesity and treat comorbidities before starting testosterone therapy.	3	C
In hypogonadal men with erectile dysfunction start with a PDE5-inhibitor as first line treatment and add testosterone in case of a poor response to PDE5i treatment.	2	A
Consider testosterone therapy in hypogonadal men with diabetes.	2	B

5.3 Choice of treatment

The aim of testosterone treatment is to restore physiological testosterone levels in hypogonadal men [106]. Several preparations are available, which differ in the route of administration, pharmacokinetics and adverse events, and the selection should be a joint decision by both the patient and the physician [107]. Short-acting preparations are preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed early and treatment can be discontinued if needed [108]. The available agents are oral preparations, intramuscular injections and transdermal gel and patches.

5.3.1 Preparations

5.3.1.1 Testosterone undecanoate

Testosterone undecanoate (TU) is the most widely used and safest oral delivery system. It rarely causes a rise in testosterone levels above the mid-range and it is therefore infrequently associated with side-effects [106]. In oral administration, resorption depends on simultaneous intake of fatty food. Testosterone undecanoate is also available as a long-acting intramuscular injection (with intervals of up to three months). This long period of action ensures a normal testosterone serum concentration for the entire period, but the relatively long wash-out period may cause problems if complications appear [109]. In the recent IPASS study, a total worldwide sample of 1,438 men was evaluated during nine to twelve months of treatment with injectable TU: TU was effective and well-tolerated, with marked improvements in several psychosexual functions and waist circumference. Adverse events and adverse drug reactions (more common: increase in hematocrit, increase in PSA, and injection site pain) were 12% and 6% respectively, mostly mild to moderate, and with no increase in prostate cancer observed [87].

5.3.1.2 Testosterone cypionate and enanthate

Testosterone cypionate and enanthate are available as short-acting intramuscular delivery systems (with intervals of 2-3 weeks) and represent safe and valid preparations. However, these preparations may cause fluctuations in serum testosterone from high levels to subnormal levels, and they are consequently associated with periods of well-being alternating with periods of unsatisfactory clinical response [110, 111]. They are also associated with increased rates of erythrocytosis.

5.3.1.3 Transdermal testosterone

Transdermal testosterone preparations are available as 1% or 2% gel. They provide a uniform and normal serum testosterone level for 24 hours (daily interval). Common side-effects are the risk of interpersonal transfer if appropriate precautions are not taken [112, 113]. The topical application of Testosterone 2% to the axillae has been demonstrated to have a safe and effective profile in a multinational open-label clinical study and has been approved in the United States and Europe [114-116]. It should be noted that patients with high BMI may require higher doses since obesity seems to affect the pharmacokinetics of transdermal testosterone preparations [117, 118].

5.3.1.4 Future perspectives

A randomised phase II clinical trial detailing the efficacy and safety of Enclomiphene Citrate (EC) as an alternative to testosterone preparations is available. Enclomiphene Citrate should provide adequate supplementation of testosterone while preventing oligospermia with a sufficient safety profile. At present it is used as an off-label medication for male hypogonadism [119-122].

5.4 Hypogonadism and fertility issues

Exogenous testosterone reduces endogenous testosterone production by negative feedback on the hypothalamic-pituitary-gonadal axis. If hypogonadism coincides with fertility issues, hCG treatment should be considered, especially in men with low gonadotropins (secondary hypogonadism). Human chorionic gonadotropin stimulates testosterone production of Leydig cells. Normal physiological serum levels can be achieved with a standard dosage of 1,500-5,000 IU administered intramuscularly or subcutaneously twice weekly. In patients with secondary hypogonadism hCG treatment is combined with FSH treatment (usually 150 IU three times weekly intramuscular or subcutaneous): to induce HCG alone may lead to suppression of FSH (negative feedback of testosterone production).

Human chorionic gonadotropin treatment has higher costs than testosterone treatment. There is insufficient information about the therapeutic and adverse effects of long-term hCG treatment. This type of treatment can therefore not be recommended for long-term treatment of male hypogonadism, except in patients in whom fertility treatment is indicated. Previous testosterone treatment does not seem to affect the efficacy of gonadotropin therapy [71, 73]. Anti-oestrogens and aromatase inhibitors are further options for hypogonadal patients with an active child wish, though evidence is limited [123].

Table 7: Testosterone preparations for replacement therapy

Formulation	Administration	Advantages	Disadvantages
Testosterone undecanoate	Oral; 2-6 cps every 6 hours	Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range [106]. Need for several doses per day with intake of fatty food.
Testosterone cypionate	Intramuscular; one injection every two to three weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Possible fluctuation of testosterone levels [110].
Testosterone enanthate	Intramuscular; one injection every two to three weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Fluctuation of testosterone levels [109, 110].
Testosterone undecanoate	Intramuscular; one injection every ten to fourteen weeks	Steady-state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects [111].
Transdermal testosterone	Gel; daily application	Steady-state testosterone level without fluctuation.	Risk of interpersonal transfer [112, 113].
Subdermal depots	Subdermal implant every five to seven months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants [106, 124, 125].

5.5 Recommendations for testosterone replacement therapy

Recommendations	LE	GR
Fully inform the patient about expected benefits and side-effects of the treatment option. Select the preparation with a joint decision by an informed patient and the physician.	3	A
Use short-acting preparations rather than long-acting depot administration when starting the initial treatment, so that therapy can be adjusted or stopped in case of adverse side-effects.	3	B
Do not use testosterone therapy in patients with male infertility and active child wish since it may suppress spermatogenesis.	1b	A
Only use human chorionic gonadotropin treatment for hypogonadotrophic hypogonadal patients with simultaneous fertility treatment.	1b	B
In patients with adult-onset hypogonadism, only prescribe testosterone treatment in men with multiple symptoms and if weight loss, lifestyle modification and good treatment balance of comorbidities have proven unsuccessful.	2	A

5.6 Risk factors in testosterone treatment

Physicians are often reluctant to offer testosterone treatment especially in elderly men due to the potential risk of this therapy. The most common doubts are represented by the possible consequences on the prostate and cardiovascular risks.

5.6.1 Male breast cancer

Male breast cancer is a rare disease with an incidence of less than 1% of all male cancers [126]. The incidence is higher in men with Klinefelter syndrome. Testosterone treatment is contraindicated in men with a history of breast cancer [31]. Association between testosterone treatment and development of breast cancer is not supported by strong evidence although there are some reports based on small numbers of patients [127].

5.6.2 Risk for prostate cancer

Prostate cancer growth may be influenced by testosterone: studies report that hypogonadism is associated with a lower incidence of prostate cancer, but if prostate cancer occurs in hypogonadal men it usually has an advanced stage and a higher Gleason score [128, 129]. Short-term randomised controlled trials support the hypothesis that testosterone treatment does not result in changes in prostatic histology nor in a significant increase in intraprostatic testosterone and DHT [130, 131]. Observational studies indicate that testosterone therapy does not increase the risk of developing prostate cancer or results in more aggressive prostate tumours [87, 130, 132, 133].

Testosterone treatment is clearly contraindicated in men with advanced prostate cancer. A topic under debate is the use of testosterone treatment in hypogonadal men with history of prostate cancer and no evidence of active disease. So far only studies with a limited number of patients and a relatively short period of follow-up are available and indicate no increased risk for prostate cancer recurrence [134, 135]. According to a recent retrospective study on hypogonadal men with previous history of prostate cancer receiving testosterone following cancer diagnosis, treatment was not associated with increased overall or cancer-specific mortality, but testosterone treatment was more likely to be prescribed in patients undergoing radical prostatectomy for well-differentiated tumours [136]. No randomised placebo-controlled trials are available yet to document its long-term safety in these patients [106]. Symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis) can be cautiously considered for testosterone treatment [137]. In these men, treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score < 8; pathological stage pT1-2; pre-operative PSA < 10 ng/ml). It is advised that therapy should not start before one year of follow-up after surgery and patients should be without PSA recurrence [138].

Patients who underwent brachytherapy or external beam radiation (EBRT) for low-risk prostate cancer can also be cautiously considered for testosterone treatment in case of symptomatic hypogonadism with a close monitoring of prostate cancer recurrence [136, 138, 139], although no long-term safety data are available in these patients.

5.6.3 Cardiovascular diseases

There is good evidence that testosterone deficiency, as well as erectile dysfunction, are both independent biomarkers, but not necessarily the cause, of cardiovascular disease and also for all-cause and cardiovascular

mortality [140]. Endogenous testosterone levels within the mid-normal range are associated with the lowest risk of mortality [92].

Two studies have reported that men with testosterone levels in the upper quartile of the normal range have a reduced number of cardiovascular events when compared to the combined data from the lower three quartiles [141, 142]. The knowledge that hypogonadism and erectile dysfunction are biomarkers of cardiovascular disease demonstrates that patients should be assessed for cardiovascular risk factors and where appropriate referred to cardiology. Individual cardiovascular risk factors (e.g. lifestyle, diet, exercise, smoking, hypertension, diabetes, dyslipidaemia) should be treated in men with pre-existing cardiovascular disease. Their secondary prevention should be optimised as best possible.

Testosterone treatment has also demonstrated in some studies beneficial effects on certain cardiovascular risk factors [143]. In men with angiographically proven coronary disease those with low testosterone are at greater risk of mortality [144, 145]. Over many years since testosterone treatment has been available up until recently, there have been no clinical studies in the medical literature, which have shown concern in regard to an increased risk of major cardiovascular events (MACE) apart from heart failure [146]. MACE is defined as the composite of cardiovascular death, non-fatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. However, three recent studies (one placebo-controlled trial [147] and two observational studies [148, 149] have suggested that testosterone treatment may be associated with an increased risk of cardiovascular events. These studies have recently been reviewed by the FDA who concluded that, 'each of the studies had major limitations, precluding the ability to draw definitive conclusions' [150]. These findings are supported by letters in response to the paper by Vigen *et al.* [151]. The controversy was fueled also by a meta-analysis by Xu *et al.* [152] of 27 small studies involving 2,994 predominantly older men that demonstrated that testosterone therapy increased the risk for cardiovascular-related events and that the effect of testosterone therapy was more dependent on the source of funding of the reported trials than on underlying baseline testosterone levels [153, 154]. However, other studies demonstrated that testosterone treatment is at least not proatherogenic over a wide range of doses [155]. In order to overcome some of the limitations of the analysis of Xu *et al.*, Corona *et al.* performed an updated systematic review and meta-analysis of RCTs on testosterone treatment, using a more conventional definition of cardiovascular events similar to that used by regulatory authorities to verify the safety of newly registered drugs (including MACE). The results do not support a causal role between testosterone treatment and adverse cardiovascular events [89].

Recent studies have provided some clarification in regard to the effect of testosterone treatment on cardiovascular events. A large (n=83,010, follow up mean > 4.7 years) retrospective study of men with low testosterone that had testosterone replaced to the normal range was associated with a reduction in myocardial infarction, whereas men treated with testosterone which did not achieve normalisation had no benefit [156]. A second retrospective analysis of MACE at three years (n=4,736) in men again treated to normalise testosterone compared groups with low, normal and high testosterone. The result was that normal testosterone reduced MACE and death [157]. A third large study (population-based matched cohort 10,311 TRT versus 28,029 controls) followed up for five years and reported that men with the highest tertile of testosterone treatment exposure decreased mortality and cardiovascular events whereas men in the lowest tertile of testosterone treatment exposure had increased mortality and cardiovascular events [94]. These studies demonstrate that when testosterone is used adequate replacement should be administered in order to normalise testosterone levels and that patients are compliant.

The European Medicines Agency (EMA) has stated 'The Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone medicines in men who lack the hormone (a condition known as hypogonadism). However, the product information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these medicines.'

A recent comprehensive and detailed meta-analysis of available evaluable randomised placebo-controlled trials concluded that the data did not support a causal role between testosterone treatment and adverse cardiovascular events [89]. There are however no long-term studies or RCTs that provide a definitive answer. Observational studies have reported that testosterone treatment improves survival when compared to men who were not treated [69, 158]. These findings are supported by a large retrospective analysis of 6,355 men treated with testosterone compared to 19,065 non-users which did not demonstrate any increased risk of myocardial infarction with testosterone treatment [159].

Caution should, however, be used in men with pre-existing cardiovascular disease. Firstly, hypogonadism must be carefully diagnosed beyond reasonable doubt. Secondly, if testosterone is prescribed then testosterone levels should not exceed the mid-normal range and the haematocrit should not exceed 0.54 [160]. Testosterone dose adjustment may be required and/or venesection (500 mL) should be considered and repeated if necessary if the haematocrit is greater than 0.54. The haematocrit value of > 54 is based on the increased risk of cardiovascular mortality from the Framingham Heart Study [161], which was recently confirmed in another study [162]. This value is also supported by the known increased risk of thrombosis in the congenital condition of idiopathic erythropoiesis [163]. The majority of patients with cardiovascular disease will be receiving anti-platelet therapy. An electrocardiogram prior to testosterone treatment in the assessment of hypogonadism could be considered.

Two large retrospective studies have not shown any evidence that testosterone treatment is associated with an increased incidence of venous thromboembolism [164, 165]. Venous thromboembolism in one study of men on testosterone treatment reported 42 (38 men) cases, 40 of which had evidence of underlying thrombophilia (which included Factor V Leiden deficiency, prothrombin mutations, homocysteinuria) of which 39 had their condition diagnosed after an event [166]. In addition, high endogenous levels of testosterone and/or oestradiol are not associated with an increased risk of venous thromboembolism [164, 165, 167]. Testosterone treatment is contraindicated in men with severe chronic cardiac failure as fluid retention may lead to an exacerbation of the condition. Some studies including one of twelve months duration have shown that men with moderate chronic cardiac failure (NYHA class III) may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [75, 168, 169]. If a decision is made to treat hypogonadism in men with chronic cardiac failure it is essential that the patient is followed carefully with clinical assessment and testosterone and hematocrit measurements, on a regular basis. An interesting observation is that testosterone deficiency increased the re-admission and mortality rate in men with heart failure [93].

5.6.4 **Obstructive sleep apnoea**

There is no consistent evidence correlating testosterone treatment with obstructive sleep apnoea (OSA). There is also no evidence that testosterone treatment can result in the onset or worsening of the condition [170].

5.6.5 **Anabolic steroid-induced hypogonadism**

Non-prescription anabolic-androgenic steroids (AAS) are used in order to obtain a boost in athletic performances. Use of AAS results in hypogonadotropic hypogonadism by feedback suppression of the hypothalamic-pituitary-gonadal (HPG) axis via inhibition of pulsatile GnRH release and a subsequent decrease in LH and FSH. The duration of suppression and the resultant symptomatic hypogonadism is highly variable and due to multiple factors, including differences in the choices of drugs, amounts used, and durations of use. After a complete endocrine and metabolic assessment, the condition may be treated with hCG, and selective oestrogen receptor modulators (SERM) [171], until the reproductive endocrine axis has been restored.

5.7 **Summary of evidence and recommendations on risk factors in testosterone replacement treatment**

Summary of evidence	LE
Case reports and small cohort studies point to a possible correlation between testosterone treatment and the onset of breast cancer, but there is as yet a lack of strong evidence for this relationship.	3
Randomised controlled trials support the hypothesis that testosterone treatment does not result in changes in prostatic histology.	1b
Recent studies indicate that testosterone treatment does not increase the risk of prostate cancer, but long-term follow-up data are not yet available.	3
There is no evidence for a relationship between testosterone treatment and obstructive sleep apnoea.	3
There is no substantive evidence that testosterone treatment, when replaced to the normal physiological range, is related to the development of major adverse cardiovascular events.	1a
In hypogonadal men testosterone treatment has been demonstrated to have a positive impact on cardiovascular risks [89].	1b

Recommendations	LE	GR
Perform haematological, cardiovascular, breast and prostatic assessment before the start of treatment.	1a	A
Monitor testosterone, haematocrit, haemoglobin and prostate-specific antigen (PSA) during testosterone treatment.	3	A
Offer testosterone treatment cautiously in symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis): treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score < 8; pathological stage pT1-2; pre-operative PSA < 10 ng/mL) and should not start before one year of follow-up.	3	B
Assess for cardiovascular risk factors before commencing testosterone treatment and optimise secondary prevention in men with pre-existing cardiovascular disease.	1a	A
Treat men with hypogonadism and either pre-existing cardiovascular disease, venous thromboembolism or chronic cardiac failure who require testosterone treatment with caution by monitoring carefully with clinical assessment, haematocrit (not exceeding 0.54) and testosterone levels maintained as best possible for age within the mid-normal healthy range.	1b	A

6. FOLLOW-UP

6.1 Monitoring of patients receiving testosterone replacement therapy

Regular follow-up is needed in patients receiving testosterone treatment, as potentially androgen-dependent symptoms and conditions may occur. The side-effects of testosterone treatment are limited, but their incidence and clinical relevance is as yet unclear. The primary aim of testosterone treatment is to alleviate the clinical symptoms of testosterone deficiency. Careful monitoring of changes in the clinical manifestations of testosterone deficiency should therefore be an essential part of every follow-up visit. Effects of testosterone treatment on sexual interest may already appear after three weeks of treatment, and reach a plateau at six weeks [76]. Changes in erectile function and ejaculation may require up to six months [76]. Effects on QoL, and also on depressive mood, may become detectable within one month, but the maximum effect may take longer [76].

6.2 Testosterone level

There are as yet insufficient data to define optimal serum levels of testosterone during testosterone treatment. Expert opinion suggests that testosterone treatment should restore the serum testosterone level to the mid-normal range of specific age groups of men, which is usually sufficient to alleviate various manifestations of hormone deficiency. An optimal monitoring schedule for serum testosterone level is also dependent on the formulation of testosterone used. It is of importance to evaluate symptom regression and lack of response prompts termination of treatment and eventual re-assessment of the diagnosis.

6.3 Bone density

Bone mineral density (BMD) should be monitored only in men whose BMD was abnormal before initiation of testosterone treatment. An increase in lumbar spine BMD may already be detectable after six months of treatment and may continue for three more years [76].

6.4 Haematocrit

It is important to use only minimal or no venous occlusion when taking a blood sample for haematocrit measurements [163]. Elevated haematocrit is the most frequent side-effect of testosterone treatment. The clinical significance of a high haematocrit level is unclear, but it may be associated with hyperviscosity and thrombosis [167]. The effect of erythropoiesis may become evident at three months and peaks at twelve months [76].

6.5 Prostate safety

Testosterone replacement therapy results in a marginal increase in PSA and prostate volume, plateauing at twelve months [76]. Previous fears that testosterone treatment might increase the risk of prostate cancer have been contradicted by a number of meta-analyses [107, 130, 134, 172]. However, there are insufficient long-term data available to conclude that there is safety regarding the development of prostate cancer with testosterone treatment. Prostate monitoring therefore remains indicated. Subjects with substantial or continuous increase of PSA level need to be investigated to exclude prostate cancer.

6.6 Cardiovascular monitoring

Caution should be used in men with pre-existing cardiovascular disease. In men with chronic heart failure, testosterone treatment can result in fluid retention and an exacerbation of the condition [168, 169]. If a decision is made to treat hypogonadism in men with chronic cardiac diseases it is essential that the patient is followed carefully with clinical assessment and testosterone and hematocrit measurements, on a regular basis.

6.7 Recommendations for follow-up

Recommendations	LE	GR
Assess the response to testosterone treatment at three, six and twelve months after the onset of treatment, and thereafter annually.	4	C
Monitor testosterone, haematocrit at three, six and twelve months and thereafter annually. Decrease the testosterone dosage or switch testosterone preparation from parenteral to topical or venesection, if haematocrit is above 0.54. If haematocrit remains elevated, stop testosterone and reintroduce at a lower dose once haematocrit has normalised.	4	C
Assess prostate health by digital rectal examination and prostate-specific antigen (PSA) before the start of testosterone replacement therapy (TRT). Follow-up by PSA tests at three, six and twelve months and thereafter annually.	4	C
Assess men with cardiovascular diseases for cardiovascular symptoms before testosterone treatment is initiated and continue close clinical assessment during treatment.	1b	A

7. REFERENCES

- Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
- 't Hoen L., *et al.* What are the risks of major cardiovascular events (MACE) from testosterone replacement therapy (TRT)? PROSPERO: International prospective register of systematic reviews, 2016.
http://www.crd.york.ac.uk/prospERO/display_record.asp?src=trip&ID=CRD42016035584
- Van den Broeck T., *et al.* What are the benefits and harms of testosterone treatment for male sexual dysfunction? PROSPERO: International prospective register of systematic reviews, 2015.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015028029
- Nieschlag, E., *et al.*, Andrology: male reproductive health and dysfunction. 3rd edn. 2010, Heidelberg.
<http://www.springer.com/us/book/9783540783541>
- Kaufman, J.M., *et al.* The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev*, 2005. 26: 833.
<https://www.ncbi.nlm.nih.gov/pubmed/15901667>
- Wu, F.C., *et al.* Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab*, 2008. 93: 2737.
<https://www.ncbi.nlm.nih.gov/pubmed/18270261>
- Hall, S.A., *et al.* Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. *J Clin Endocrinol Metab*, 2008. 93: 3870.
<https://www.ncbi.nlm.nih.gov/pubmed/18664536>
- Nieschlag, E., *et al.*, Testosterone: action, deficiency, substitution. 2004, 3rd ed. Cambridge.
<http://www.andrology.org/books/37-isa-library/books/114-testosterone-action-deficiency-substitution>
- Parker, K.L., *et al.* Genes essential for early events in gonadal development. *Cell Mol Life Sci*, 1999. 55: 831.
<https://www.ncbi.nlm.nih.gov/pubmed/10412366>

10. Brinkmann, A.O. Molecular mechanisms of androgen action--a historical perspective. *Methods Mol Biol*, 2011. 776: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/21796517>
11. Bentvelsen, F.M., *et al.* The androgen receptor of the urogenital tract of the fetal rat is regulated by androgen. *Mol Cell Endocrinol*, 1994. 105: 21.
<https://www.ncbi.nlm.nih.gov/pubmed/7821714>
12. Singh, J., *et al.* Induction of spermatogenesis by androgens in gonadotropin-deficient (hpg) mice. *Endocrinology*, 1995. 136: 5311.
<https://www.ncbi.nlm.nih.gov/pubmed/7588276>
13. Sun, Y.T., *et al.* The effects of exogenously administered testosterone on spermatogenesis in intact and hypophysectomized rats. *Endocrinology*, 1989. 125: 1000.
<https://www.ncbi.nlm.nih.gov/pubmed/2502373>
14. Weinbauer, G.F., *et al.* Gonadotrophin-releasing hormone analogue-induced manipulation of testicular function in the monkey. *Hum Reprod*, 1993. 8 Suppl 2: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/8276968>
15. McLachlan, R.I., *et al.* Hormonal regulation of spermatogenesis in primates and man: insights for development of the male hormonal contraceptive. *J Androl*, 2002. 23: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/11868805>
16. de Ronde, W., *et al.* Aromatase inhibitors in men: effects and therapeutic options. *Reprod Biol Endocrinol*, 2011. 9: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/21693046>
17. Brinkmann, A.O. Molecular basis of androgen insensitivity. *Mol Cell Endocrinol*, 2001. 179: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/11420135>
18. Zitzmann, M. Mechanisms of disease: pharmacogenetics of testosterone therapy in hypogonadal men. *Nat Clin Pract Urol*, 2007. 4: 161.
<https://www.ncbi.nlm.nih.gov/pubmed/17347661>
19. Rajender, S., *et al.* Phenotypic heterogeneity of mutations in androgen receptor gene. *Asian J Androl*, 2007. 9: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/17334586>
20. Canale, D., *et al.* Androgen receptor polymorphism (CAG repeats) and androgenicity. *Clin Endocrinol (Oxf)*, 2005. 63: 356.
<https://www.ncbi.nlm.nih.gov/pubmed/16117826>
21. Bojesen, A., *et al.* Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab*, 2003. 88: 622.
<https://www.ncbi.nlm.nih.gov/pubmed/12574191>
22. Tuttelmann, F., *et al.* Novel genetic aspects of Klinefelter's syndrome. *Mol Hum Reprod*, 2010. 16: 386.
<https://www.ncbi.nlm.nih.gov/pubmed/20228051>
23. Eberhard, J., *et al.* Risk factors for post-treatment hypogonadism in testicular cancer patients. *Eur J Endocrinol*, 2008. 158: 561.
<https://www.ncbi.nlm.nih.gov/pubmed/18362304>
24. Puhse, G., *et al.* Testosterone deficiency in testicular germ-cell cancer patients is not influenced by oncological treatment. *Int J Androl*, 2011. 34: e351.
<https://www.ncbi.nlm.nih.gov/pubmed/21062302>
25. Abouassaly, R., *et al.* Sequelae of treatment in long-term survivors of testis cancer. *Eur Urol*, 2011. 60: 516.
<https://www.ncbi.nlm.nih.gov/pubmed/21684072>
26. Shimon I., *et al.* Male prolactinomas presenting with normal testosterone levels. *Pituitary*, 2014. 17: 246.
<https://www.ncbi.nlm.nih.gov/pubmed/23756784>
27. Behre, H., *et al.*, *Andrology - male reproductive health and dysfunction*. 3rd edn., in Springer. 2010: Berlin.
<http://www.springer.com/us/book/9783540783541>
28. Pitteloud, N., *et al.* Complex genetics in idiopathic hypogonadotropic hypogonadism. *Front Horm Res*, 2010. 39: 142.
<https://www.ncbi.nlm.nih.gov/pubmed/20389092>
29. Sedlmeyer, I.L., *et al.* Pedigree analysis of constitutional delay of growth and maturation: determination of familial aggregation and inheritance patterns. *J Clin Endocrinol Metab*, 2002. 87: 5581.
<https://www.ncbi.nlm.nih.gov/pubmed/12466356>

30. Nieschlag, E., *et al.* Investigation, treatment and monitoring of late-onset hypogonadism in males. ISA, ISSAM, and EAU recommendations. *Eur Urol*, 2005. 48: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/15951102>
31. Wang, C., *et al.* Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *Eur Urol*, 2009. 55: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/18762364>
32. Kelsey, T.W., *et al.* A validated age-related normative model for male total testosterone shows increasing variance but no decline after age 40 years. *PLoS One*, 2014. 9: e109346.
<https://www.ncbi.nlm.nih.gov/pubmed/25295520>
33. Nieschlag, E., *et al.*, Disorders at the testicular level. In: *Andrology - male reproductive health and dysfunction*. 2010, 3rd edn. Springer: Berlin.
<http://www.springer.com/us/book/9783540783541>
34. Buchter, D., *et al.* Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases. *Eur J Endocrinol*, 1998. 139: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/9758439>
35. Sykiotis, G.P., *et al.* Congenital idiopathic hypogonadotropic hypogonadism: evidence of defects in the hypothalamus, pituitary, and testes. *J Clin Endocrinol Metab*, 2010. 95: 3019.
<https://www.ncbi.nlm.nih.gov/pubmed/20382682>
36. Huhtaniemi, I., *et al.* Gonadotrophin resistance. *Best Pract Res Clin Endocrinol Metab*, 2006. 20: 561.
<https://www.ncbi.nlm.nih.gov/pubmed/17161332>
37. Bhasin, S., *et al.* Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*, 2010. 95: 2536.
<https://www.ncbi.nlm.nih.gov/pubmed/20525905>
38. Rosner, W., *et al.* Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab*, 2007. 92: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/17090633>
39. Rosner, W., *et al.* Toward excellence in testosterone testing: a consensus statement. *J Clin Endocrinol Metab*, 2010. 95: 4542.
<https://www.ncbi.nlm.nih.gov/pubmed/20926540>
40. Wang, C., *et al.* Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography-tandem mass spectrometry. *J Clin Endocrinol Metab*, 2004. 89: 534.
<https://www.ncbi.nlm.nih.gov/pubmed/14764758>
41. Rastrelli G., *et al.* Development of and Recovery from Secondary Hypogonadism in Aging Men: Prospective Results from the EMAS. *J Clin Endocrinol Metab*, 2015. 100: 3172.
<https://www.ncbi.nlm.nih.gov/pubmed/26000545>
42. Bhasin, S., *et al.* Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab*, 2001. 281: E1172.
<https://www.ncbi.nlm.nih.gov/pubmed/11701431>
43. Wu, F.C., *et al.* Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*, 2010. 363: 123.
<https://www.ncbi.nlm.nih.gov/pubmed/20554979>
44. Bhasin, S., *et al.* Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. *J Clin Endocrinol Metab*, 2011. 96: 2430.
<https://www.ncbi.nlm.nih.gov/pubmed/21697255>
45. Vesper, H.W., *et al.* Interlaboratory comparison study of serum total testosterone [corrected] measurements performed by mass spectrometry methods. *Steroids*, 2009. 74: 498.
<https://www.ncbi.nlm.nih.gov/pubmed/19428438>
46. Ahern T., *et al.* New horizons in testosterone and the ageing male. *Age Ageing*. 2015, 44: 188.
<https://www.ncbi.nlm.nih.gov/pubmed/>
47. Bremner, W.J., *et al.* Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab*, 1983. 56: 1278.
<https://www.ncbi.nlm.nih.gov/pubmed/6841562>
48. Morales A. Testosterone Deficiency Syndrome: An overview with emphasis on the diagnostic conundrum. *Clin Biochem*. 2014. 47: 960.
<https://www.ncbi.nlm.nih.gov/pubmed/24355693>

49. Berookhim B, *et al.* Intra-individual variations in serum total testosterone among men presenting for evaluation of hypogonadism. *J Urol*, 2014. 191 (41) e334, 2014.
[https://www.ncbi.nlm.nih.gov/pubmed/http://www.jurology.com/article/S0022-5347\(14\)01201-4/abstract](https://www.ncbi.nlm.nih.gov/pubmed/http://www.jurology.com/article/S0022-5347(14)01201-4/abstract)
50. Buvat, J., *et al.* Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost-effective strategy. *J Urol*, 1997. 158: 1764.
<https://www.ncbi.nlm.nih.gov/pubmed/9334596>
51. Moore, C., *et al.* The Aging Males' Symptoms scale (AMS) as outcome measure for treatment of androgen deficiency. *Eur Urol*, 2004. 46: 80.
<https://www.ncbi.nlm.nih.gov/pubmed/15183551>
52. Morley, J.E., *et al.* Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism*, 2000. 49: 1239.
<https://www.ncbi.nlm.nih.gov/pubmed/11016912>
53. Smith, K.W., *et al.* Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. *Clin Endocrinol (Oxf)*, 2000. 53: 703.
<https://www.ncbi.nlm.nih.gov/pubmed/11155092>
54. Birthi P., *et al.* Hypogonadism associated with long-term opioid therapy: A systematic review. *J Opioid Manag*, 2015. 11: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/25985810>
55. Basaria S., *et al.* Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. *Pain*, 2015. 156: 280.
<https://www.ncbi.nlm.nih.gov/pubmed/25599449>
56. Traggiai, C., *et al.* Delayed puberty. *Best Pract Res Clin Endocrinol Metab*, 2002. 16: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/11987904>
57. Lanfranco, F., *et al.* Klinefelter's syndrome. *Lancet*, 2004. 364: 273.
<https://www.ncbi.nlm.nih.gov/pubmed/15262106>
58. Zitzmann, M., *et al.* Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab*, 2006. 91: 4335.
<https://www.ncbi.nlm.nih.gov/pubmed/16926258>
59. Schneider, G., *et al.* Aging males' symptoms in relation to the genetically determined androgen receptor CAG polymorphism, sex hormone levels and sample membership. *Psychoneuroendocrinology*, 2010. 35: 578.
<https://www.ncbi.nlm.nih.gov/pubmed/19804943>
60. Zitzmann, M., *et al.* The CAG repeat polymorphism within the androgen receptor gene and maleness. *Int J Androl*, 2003. 26: 76.
<https://www.ncbi.nlm.nih.gov/pubmed/12641825>
61. Kapoor, D., *et al.* Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. *Diabetes Care*, 2007. 30: 911.
<https://www.ncbi.nlm.nih.gov/pubmed/17392552>
62. Dhindsa, S., *et al.* Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab*, 2004. 89: 5462.
<https://www.ncbi.nlm.nih.gov/pubmed/15531498>
63. Ding, E.L., *et al.* Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *Jama*, 2006. 295: 1288.
<https://www.ncbi.nlm.nih.gov/pubmed/16537739>
64. Kalinchenko, S.Y., *et al.* Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male*, 2003. 6: 94.
<https://www.ncbi.nlm.nih.gov/pubmed/12898793>
65. Jones, T.H., *et al.* Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care*, 2011. 34: 828.
<https://www.ncbi.nlm.nih.gov/pubmed/21386088>
66. Hackett G, *et al.* Testosterone Undecanoate improves Sexual Function in Men with Type 2 diabetes and Severe Hypogonadism: Results from a 30 week randomized placebo controlled study. *BJU Int*, 2016. 118: 804.
<https://www.ncbi.nlm.nih.gov/pubmed/27124889>
67. Giltay, E.J., *et al.* Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. *J Sex Med*, 2010. 7: 2572.
<https://www.ncbi.nlm.nih.gov/pubmed/20524974>

68. Gianatti, E.J., *et al.* Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. *J Clin Endocrinol Metab*, 2014. 99: 3821.
<https://www.ncbi.nlm.nih.gov/pubmed/24978674>
69. Muraleedharan, V., *et al.* Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol*, 2013. 169: 725.
<https://www.ncbi.nlm.nih.gov/pubmed/23999642>
70. Rao, P.M., *et al.* Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. *Nat Rev Endocrinol*, 2013. 9: 479.
<https://www.ncbi.nlm.nih.gov/pubmed/23797822>
71. Rastrelli G, *et al.* Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. *Andrology*, 2014. 2: 794.
<https://www.ncbi.nlm.nih.gov/pubmed/25271205>
72. Dwyer A. A., *et al.* Psychosexual Development in Men with Congenital Hypogonadotropic Hypogonadism on Long-Term Treatment: A Mixed Methods Study. *Sex Med*, 2015. 3: 32.
<https://www.ncbi.nlm.nih.gov/pubmed/25844173>
73. Rohayem, J., *et al.* Testicular growth and spermatogenesis: new goals for pubertal hormone replacement in boys with hypogonadotropic hypogonadism? -a multicentre prospective study of hCG/rFSH treatment outcomes during adolescence. *Clin Endocrinol (Oxf)*, 2017. 86: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/27467188>
- 74a. Camacho, E.M., *et al.* Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *Eur J Endocrinol*, 2013. 168: 445.
<https://www.ncbi.nlm.nih.gov/pubmed/23425925>
- 74b. Kumagai, H., *et al.* Lifestyle modification increases serum testosterone level and decrease central blood pressure in overweight and obese men. *Endocr J*, 2015. 62: 423.
<https://www.ncbi.nlm.nih.gov/pubmed/25753766>
75. Caminiti, G., *et al.* Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol*, 2009. 54: 919.
<https://www.ncbi.nlm.nih.gov/pubmed/19712802>
76. Saad, F., *et al.* Onset of effects of testosterone treatment and time span until maximum effects are achieved. *Eur J Endocrinol*, 2011. 165: 675.
<https://www.ncbi.nlm.nih.gov/pubmed/21753068>
77. Storer, T.W., *et al.* Changes in muscle mass, muscle strength, and power but not physical function are related to testosterone dose in healthy older men. *J Am Geriatr Soc*, 2008. 56: 1991.
<https://www.ncbi.nlm.nih.gov/pubmed/18795988>
78. Bello A. K., *et al.* Serum testosterone levels and clinical outcomes in male hemodialysis patients. *Am J Kidney Dis*, 2014. 63: 268.
<https://www.ncbi.nlm.nih.gov/pubmed/23896484>
79. Isidori, A.M., *et al.* Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)*, 2005. 63: 280.
<https://www.ncbi.nlm.nih.gov/pubmed/16117815>
80. Tracz, M.J., *et al.* Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. *J Clin Endocrinol Metab*, 2006. 91: 2011.
<https://www.ncbi.nlm.nih.gov/pubmed/16720668>
81. Irwig, M.S. Bone health in hypogonadal men. *Curr Opin Urol*, 2014. 24: 608.
<https://www.ncbi.nlm.nih.gov/pubmed/25144148>
82. Shanbhogue V. V, *et al.* Bone geometry, volumetric density, microarchitecture, and estimated bone strength assessed by HR-pQCT in Klinefelter syndrome. *J Bone Miner Res*, 2015, 30: 2188.
<https://www.ncbi.nlm.nih.gov/pubmed/26096924>
83. Kelly, D.M., *et al.* Testosterone and obesity. *Obes Rev*, 2015. 16: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/25982085>
84. Gaffney, C.D., *et al.* Osteoporosis and Low Bone Mineral Density in Men with Testosterone Deficiency Syndrome. *Sex Med Rev*, 2015. 3: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/27784602>

85. Saad, F., *et al.* Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. *Obesity (Silver Spring)*, 2013. 21: 1975.
<https://www.ncbi.nlm.nih.gov/pubmed/23512691>
86. Traish, A.M., *et al.* Long-term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. *Int J Clin Pract*, 2014. 68: 314.
<https://www.ncbi.nlm.nih.gov/pubmed/24127736>
87. Zitzmann, M., *et al.* IPASS: a study on the tolerability and effectiveness of injectable testosterone undecanoate for the treatment of male hypogonadism in a worldwide sample of 1,438 men. *J Sex Med*, 2013. 10: 579.
<https://www.ncbi.nlm.nih.gov/pubmed/22812645>
88. Araujo, A.B., *et al.* Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab*, 2011. 96: 3007.
<https://www.ncbi.nlm.nih.gov/pubmed/21816776>
89. Corona, G., *et al.* Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf*, 2014. 13: 1327.
<https://www.ncbi.nlm.nih.gov/pubmed/25139126>
90. Haring, R., *et al.* Association of low testosterone levels with all-cause mortality by different cut-offs from recent studies. *Eur Heart J*, 2010. 31.
91. Morgentaler, A. Testosterone, cardiovascular risk, and hormonophobia. *J Sex Med*, 2014. 11: 1362.
<https://www.ncbi.nlm.nih.gov/pubmed/24787518>
92. Yeap, B.B., *et al.* In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. *J Clin Endocrinol Metab*, 2014. 99: E9.
<https://www.ncbi.nlm.nih.gov/pubmed/24257908>
93. Santos M. R., *et al.* Testosterone deficiency increases hospital readmission and mortality rates in male patients with heart failure. *Arq Bras Cardiol*, 2015. 105:256.
<https://www.ncbi.nlm.nih.gov/pubmed/26200897>
94. Wallis, C.J., *et al.* Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. *Lancet Diabetes Endocrinol*, 2016. 4: 498.
<https://www.ncbi.nlm.nih.gov/pubmed/27165609>
95. Zarotsky V, *et al.* Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. *Andrology*, 2014. 2: 819.
<https://www.ncbi.nlm.nih.gov/pubmed/25269643>
96. Basaria S., *et al.* Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. *JAMA*, 2015. 314: 570.
<https://www.ncbi.nlm.nih.gov/pubmed/26262795>
97. Isidori A. M., *et al.* A critical analysis of the role of testosterone in erectile function: From pathophysiology to treatment - A systematic review. *Eur Urol*, 2014. 65: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/24050791>
98. Snyder, P.J., *et al.* Effects of Testosterone Treatment in Older Men. *N Engl J Med*, 2016. 374: 611.
<https://www.ncbi.nlm.nih.gov/pubmed/26886521>
99. Brock G, *et al.* Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study. *J Urol*, 2016. 195: 699.
<https://www.ncbi.nlm.nih.gov/pubmed/26498057>
100. Hackett, G., *et al.* Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. *J Sex Med*, 2013. 10: 1612.
<https://www.ncbi.nlm.nih.gov/pubmed/23551886>
101. Corona G, *et al.* Testosterone supplementation and sexual function: A meta-analysis study. *Andrology*. Conference: 8th Congress of the European Academy of Andrology Barcelona Spain. 2 (pp 37), 2014.
102. Mulhall J. P, *et al.* Impact of Baseline Total Testosterone Level on Successful Treatment of Sexual Dysfunction in Men Taking Once-Daily Tadalafil 5 mg for Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia: An Integrated Analysis of Three Randomized Controlled Trials. *J Sex Med*, 2016. 13: 843.
<https://www.ncbi.nlm.nih.gov/pubmed/27017071>
103. Spitzer M, *et al.* Sildenafil increases serum testosterone levels by a direct action on the testes. *Andrology*, 2013. 1: 913.
<https://www.ncbi.nlm.nih.gov/pubmed/24106072>

104. Cherrier M. M, *et al.* Testosterone Treatment of Men With Mild Cognitive Impairment and Low Testosterone Levels. *Am J Alzheimers Dis Other Demen*, 2015. 30: 421.
<https://www.ncbi.nlm.nih.gov/pubmed/25392187>
105. Amanatkar, H.R., *et al.* Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. *Ann Clin Psychiatry*, 2014. 26: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/24501728>
106. Bassil, N., *et al.* The benefits and risks of testosterone replacement therapy: a review. *Ther Clin Risk Manag*, 2009. 5: 427.
<https://www.ncbi.nlm.nih.gov/pubmed/19707253>
107. Calof, O.M., *et al.* Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci*, 2005. 60: 1451.
<https://www.ncbi.nlm.nih.gov/pubmed/16339333>
108. Parsons, J.K., *et al.* Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiol Biomarkers Prev*, 2005. 14: 2257.
<https://www.ncbi.nlm.nih.gov/pubmed/16172240>
109. Wang, C., *et al.* Pharmacokinetics and safety of long-acting testosterone undecanoate injections in hypogonadal men: an 84-week phase III clinical trial. *J Androl*, 2010. 31: 457.
<https://www.ncbi.nlm.nih.gov/pubmed/20133964>
110. Bhasin, S., *et al.* Clinical review 85: Emerging issues in androgen replacement therapy. *J Clin Endocrinol Metab*, 1997. 82: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/8989221>
111. Comhaire, F.H. Andropause: hormone replacement therapy in the ageing male. *Eur Urol*, 2000. 38: 655.
<https://www.ncbi.nlm.nih.gov/pubmed/11111180>
112. Lakshman, K.M., *et al.* Safety and efficacy of testosterone gel in the treatment of male hypogonadism. *Clin Interv Aging*, 2009. 4: 397.
<https://www.ncbi.nlm.nih.gov/pubmed/19966909>
113. Swerdloff, R.S., *et al.* Transdermal androgens: pharmacology and applicability to hypogonadal elderly men. *J Endocrinol Invest*, 2005. 28: 112.
<https://www.ncbi.nlm.nih.gov/pubmed/16042369>
114. Muram, D., *et al.* Comparability of single measurements of serum testosterone to the 24-hour cavg in patients using testosterone 2% solution. *J Sex Med*, 2014. 11: 2826.
<https://www.ncbi.nlm.nih.gov/pubmed/25123851>
115. Muram, D., *et al.* Skin reactions in a phase 3 study of a testosterone topical solution applied to the axilla in hypogonadal men. *Curr Med Res Opin*, 2012. 28: 761.
<https://www.ncbi.nlm.nih.gov/pubmed/22458919>
116. Wang, C., *et al.* Efficacy and safety of the 2% formulation of testosterone topical solution applied to the axillae in androgen-deficient men. *Clin Endocrinol (Oxf)*, 2011. 75: 836.
<https://www.ncbi.nlm.nih.gov/pubmed/21689131>
117. Dobs A, *et al.* Testosterone 2% gel can normalize testosterone concentrations in men with low testosterone regardless of body mass index. *J Sex Med*, 2014. 11: 857.
<https://www.ncbi.nlm.nih.gov/pubmed/24283410>
118. Winter A, *et al.* Predictors of poor response to transdermal testosterone therapy in men with metabolic syndrome. *J Urol*, 2014. 191: e528.
[http://www.jurology.com/article/S0022-5347\(14\)01736-4/abstract](http://www.jurology.com/article/S0022-5347(14)01736-4/abstract)
119. Ramasamy, R., *et al.* Testosterone supplementation versus clomiphene citrate for hypogonadism: an age matched comparison of satisfaction and efficacy. *J Urol*, 2014. 192: 875.
<https://www.ncbi.nlm.nih.gov/pubmed/24657837>
120. Wiehle, R.D., *et al.* Enclomiphene citrate stimulates testosterone production while preventing oligospermia: a randomized phase II clinical trial comparing topical testosterone. *Fertil Steril*, 2014. 102: 720.
<https://www.ncbi.nlm.nih.gov/pubmed/25044085>
121. Wiehle R, *et al.* Testosterone restoration using enclomiphene citrate in men with secondary hypogonadism: A pharmacodynamic and pharmacokinetic study. *BJU Int*, 2013.
<https://www.ncbi.nlm.nih.gov/pubmed/23875626>
122. Wiehle R. D, *et al.* Enclomiphene citrate stimulates serum testosterone in men with low testosterone within 14 days. *J Mens Health*, 2014. 11: 1.
<https://www.researchgate.net/publication/271134289>

123. Ho C. C. K, *et al.* Treatment of the hypogonadal infertile male - A review. *Sex Med Rev*, 2013. 1: 42. <https://www.ncbi.nlm.nih.gov/pubmed/27784559>
124. Jockenhovel, F., *et al.* Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men. *Clin Endocrinol (Oxf)*, 1996. 45: 61. <https://www.ncbi.nlm.nih.gov/pubmed/8796140>
125. Kelleher, S., *et al.* Influence of implantation site and track geometry on the extrusion rate and pharmacology of testosterone implants. *Clin Endocrinol (Oxf)*, 2001. 55: 531. <https://www.ncbi.nlm.nih.gov/pubmed/11678837>
126. Johansen Taber, K.A., *et al.* Male breast cancer: risk factors, diagnosis, and management (Review). *Oncol Rep*, 2010. 24: 1115. <https://www.ncbi.nlm.nih.gov/pubmed/20878100>
127. Medras, M., *et al.* Breast cancer and long-term hormonal treatment of male hypogonadism. *Breast Cancer Res Treat*, 2006. 96: 263. <https://www.ncbi.nlm.nih.gov/pubmed/16418796>
128. Severi, G., *et al.* Circulating steroid hormones and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*, 2006. 15: 86. <https://www.ncbi.nlm.nih.gov/pubmed/16434592>
129. Stattin, P., *et al.* High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. *Int J Cancer*, 2004. 108: 418. <https://www.ncbi.nlm.nih.gov/pubmed/14648709>
130. Marks, L.S., *et al.* Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA*, 2006. 296: 2351. <https://www.ncbi.nlm.nih.gov/pubmed/17105798>
131. Thirumalai A, *et al.* Stable Intraprostatic Dihydrotestosterone in Healthy Medically Castrate Men Treated with Exogenous Testosterone. *J Clin Endocrinol Metab*, 2016 101: 2937. <https://www.ncbi.nlm.nih.gov/pubmed/27172434>
132. Cooper, C.S., *et al.* Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. *J Urol*, 1998. 159: 441. <https://www.ncbi.nlm.nih.gov/pubmed/9649259>
133. Baillargeon, J., *et al.* Long-term Exposure to Testosterone Therapy and the Risk of High Grade Prostate Cancer. *J Urol*, 2015. 194: 1612. <https://www.ncbi.nlm.nih.gov/pubmed/26066403>
134. Shabsigh, R., *et al.* Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review. *Int J Impot Res*, 2009. 21: 9. <https://www.ncbi.nlm.nih.gov/pubmed/18633357>
135. Kaplan, A.L., *et al.* Testosterone Therapy in Men With Prostate Cancer. *Eur Urol*, 2016. 69: 894. <https://www.ncbi.nlm.nih.gov/pubmed/26719015>
136. Kaplan, A.L., *et al.* Testosterone replacement therapy following the diagnosis of prostate cancer: outcomes and utilization trends. *J Sex Med*, 2014. 11: 1063. <https://www.ncbi.nlm.nih.gov/pubmed/24443943>
137. Aversa, A., *et al.* Cardiometabolic complications after androgen deprivation therapy in a man with prostate cancer: effects of 3 years intermittent testosterone supplementation. *Front Endocrinol (Lausanne)*, 2012. 3: 17. <https://www.ncbi.nlm.nih.gov/pubmed/22645517>
138. Kaufman, J.M., *et al.* Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *J Urol*, 2004. 172: 920. <https://www.ncbi.nlm.nih.gov/pubmed/15310998>
139. Sarosdy, M.F. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer*, 2007. 109: 536. <https://www.ncbi.nlm.nih.gov/pubmed/17183557>
140. Muraleedharan, V., *et al.* Testosterone and mortality. *Clin Endocrinol (Oxf)*, 2014. 81: 477. <https://www.ncbi.nlm.nih.gov/pubmed/25041142>
141. Ohlsson, C., *et al.* High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. *J Am Coll Cardiol*, 2011. 58: 1674. <https://www.ncbi.nlm.nih.gov/pubmed/21982312>
142. Soisson, V., *et al.* A J-shaped association between plasma testosterone and risk of ischemic arterial event in elderly men: the French 3C cohort study. *Maturitas*, 2013. 75: 282. <https://www.ncbi.nlm.nih.gov/pubmed/23706278>

143. Jones, T.H. Testosterone deficiency: a risk factor for cardiovascular disease? *Trends Endocrinol Metab*, 2010. 21: 496.
<https://www.ncbi.nlm.nih.gov/pubmed/20381374>
144. Corona, G., *et al.* Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol*, 2011. 165: 687.
<https://www.ncbi.nlm.nih.gov/pubmed/21852391>
145. Malkin, C.J., *et al.* Low serum testosterone and increased mortality in men with coronary heart disease. *Heart*, 2010. 96: 1821.
<https://www.ncbi.nlm.nih.gov/pubmed/20959649>
146. Haddad, R.M., *et al.* Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc*, 2007. 82: 29.
<https://www.ncbi.nlm.nih.gov/pubmed/17285783>
147. Basaria, S., *et al.* Adverse events associated with testosterone administration. *N Engl J Med*, 2010. 363: 109.
<https://www.ncbi.nlm.nih.gov/pubmed/20592293>
148. Finkle, W.D., *et al.* Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*, 2014. 9: e85805.
<https://www.ncbi.nlm.nih.gov/pubmed/24489673>
149. Vigen, R., *et al.* Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*, 2013. 310: 1829.
<https://www.ncbi.nlm.nih.gov/pubmed/24193080>
150. FDA. Briefing Information for the September 17, 2014 Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting.
<http://www.fda.gov/AdvisoryCommittees/ucm404905.htm>
151. FDA. Advisory committee industry briefing document. Testosterone therapy. Bone, reproductive and urologic drugs advisory committee and the drug safety and risk management advisory committee. 2014.
<http://www.fda.gov/downloads/AdvisoryCommittee/.../UCM412537.pdf>
152. Xu, L., *et al.* Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*, 2013. 11: 108.
<https://www.ncbi.nlm.nih.gov/pubmed/23597181>
153. Yuen K. C. J. Testosterone and cardiovascular disease: Controversy or wake-up call? *Cardiovascular Endocrinol*, 2014. 3: 117.
<http://universalmensclinic.com/wp-content/uploads/2014/10/TRT-CVD-review-paper-Sept-2014.pdf>
154. Schooling, C.M. Testosterone and cardiovascular disease. *Curr Opin Endocrinol Diabetes Obes*, 2014. 21: 202.
<https://www.ncbi.nlm.nih.gov/pubmed/24722171>
155. Roberts C. K, *et al.* Effects of varying doses of testosterone on atherogenic markers in healthy younger and older men. *Am J Physiol Regul Integr Comp Physiol*, 2014. 306: R118.
<https://www.ncbi.nlm.nih.gov/pubmed/24305063>
156. Sharma, R., *et al.* Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J*, 2015. 36: 2706.
<https://www.ncbi.nlm.nih.gov/pubmed/26248567>
157. Anderson, J.L., *et al.* Impact of Testosterone Replacement Therapy on Myocardial Infarction, Stroke, and Death in Men With Low Testosterone Concentrations in an Integrated Health Care System. *Am J Cardiol*, 2016. 117: 794.
<https://www.ncbi.nlm.nih.gov/pubmed/26772440>
158. Shores, M.M., *et al.* Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab*, 2012. 97: 2050.
<https://www.ncbi.nlm.nih.gov/pubmed/22496507>
159. Baillargeon, J., *et al.* Risk of Myocardial Infarction in Older Men Receiving Testosterone Therapy. *Ann Pharmacother*, 2014. 48: 1138.
<https://www.ncbi.nlm.nih.gov/pubmed/26066403>
160. Jones S. D., *et al.* Erythrocytosis and Polycythemia Secondary to Testosterone Replacement Therapy in the Aging Male. *Sex Med Rev*, 2015. 3: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/27784544>
161. Gagnon, D.R., *et al.* Hematocrit and the risk of cardiovascular disease--the Framingham study: a 34-year follow-up. *Am Heart J*, 1994. 127: 674.
<https://www.ncbi.nlm.nih.gov/pubmed/Gagnon>

162. Boffetta, P., *et al.* A U-shaped relationship between haematocrit and mortality in a large prospective cohort study. *Int J Epidemiol*, 2013. 42: 601.
<https://www.ncbi.nlm.nih.gov/pubmed/23569195>
163. McMullin, M.F., *et al.* Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol*, 2005. 130: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/16029446>
164. Baillargeon, J., *et al.* Risk of Venous Thromboembolism in Men Receiving Testosterone Therapy. *Mayo Clin Proc*, 2015. 90: 1038.
<https://www.ncbi.nlm.nih.gov/pubmed/26205547>
165. Sharma, R., *et al.* Association Between Testosterone Replacement Therapy and the Incidence of DVT and Pulmonary Embolism: A Retrospective Cohort Study of the Veterans Administration Database. *Chest*, 2016. 150: 563.
<https://www.ncbi.nlm.nih.gov/pubmed/27179907>
166. Glueck, C.J., *et al.* Testosterone therapy, thrombosis, thrombophilia, cardiovascular events. *Metabolism*, 2014. 63: 989.
<https://www.ncbi.nlm.nih.gov/pubmed/24930993>
167. Holmegard, H.N., *et al.* Endogenous sex hormones and risk of venous thromboembolism in women and men. *J Thromb Haemost*, 2014. 12: 297.
<https://www.ncbi.nlm.nih.gov/pubmed/24329981>
168. Malkin, C.J., *et al.* Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J*, 2006. 27: 57.
<https://www.ncbi.nlm.nih.gov/pubmed/16093267>
169. Pugh, P.J., *et al.* Testosterone treatment for men with chronic heart failure. *Heart*, 2004. 90: 446.
<https://www.ncbi.nlm.nih.gov/pubmed/15020527>
170. Hanafy, H.M. Testosterone therapy and obstructive sleep apnea: is there a real connection? *J Sex Med*, 2007. 4: 1241.
<https://www.ncbi.nlm.nih.gov/pubmed/17645445>
171. Rahnema C. D, *et al.* Anabolic steroid-induced hypogonadism: Diagnosis and treatment. *Fertil Steril*, 2014. 101: 1271.
<https://www.ncbi.nlm.nih.gov/pubmed/24636400>
172. Fernandez-Balsells, M.M., *et al.* Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab*, 2010. 95: 2560.
<https://www.ncbi.nlm.nih.gov/pubmed/20525906>

8. CONFLICT OF INTEREST

All members of the EAU Male Hypogonadism Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guideline/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Urological Infections

G. Bonkat (Co-chair), R. Pickard (Co-chair), R. Bartoletti,
F. Bruyère, S.E. Geerlings, F. Wagenlehner, B. Wullt
Guidelines Associates: T. Cai, B. Köves, A. Pilatz,
B. Pradere, R. Veeratterapillay

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Urological Infections Guidelines Panel has compiled these clinical guidelines to provide medical professionals with evidence-based information and recommendations for the prevention and treatment of urological tract infections (UTIs). These guidelines also aim to address the important public health aspects of infection control and antimicrobial stewardship. Separate EAU guidelines documents are available addressing paediatric urological infections [1] and infections in patients with neurological urinary tract dysfunction [2].

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urological Infections Guidelines Panel consists of a multi-disciplinary group of urologists, with particular expertise in this area, and an infectious disease specialist. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/urological-infections/>.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions, which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: <http://uroweb.org/guideline/urologicalinfections/>.

1.4 Publication history

The Urological Infections Guidelines were first published in 2001. The 2016 document consisted of the first completed sections of an entirely new Urological Infections Guideline formulated following new EAU guideline production methodology. This 2017 document is an amalgamation of the 2015 and 2016 Guidelines and will be updated over the coming year to cover all key clinical questions related to UTIs.

2. METHODS

2.1 Introduction

For the 2017 Urological Infections Guidelines, specific chapters were updated based on systematic reviews of topics or questions prioritised by the Guideline Panel. These reviews were performed using standard Cochrane systematic review methodology, <http://www.cochranelibrary.com/about/about-cochrane-systematicreviews.html>.

Systematic review results for the following evidence questions are included in the 2017 Urological Infections Guidelines:

1. What is the most effective management for adults with asymptomatic bacteriuria [3]?
2. What is the best antimicrobial prophylaxis strategy to reduce risk of infectious complication of prostate biopsy [4]?

References used in this text are graded according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional information can be found in the general Methodology section of this print, and online at the EAU website: <http://www.uroweb.org/guideline/>. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

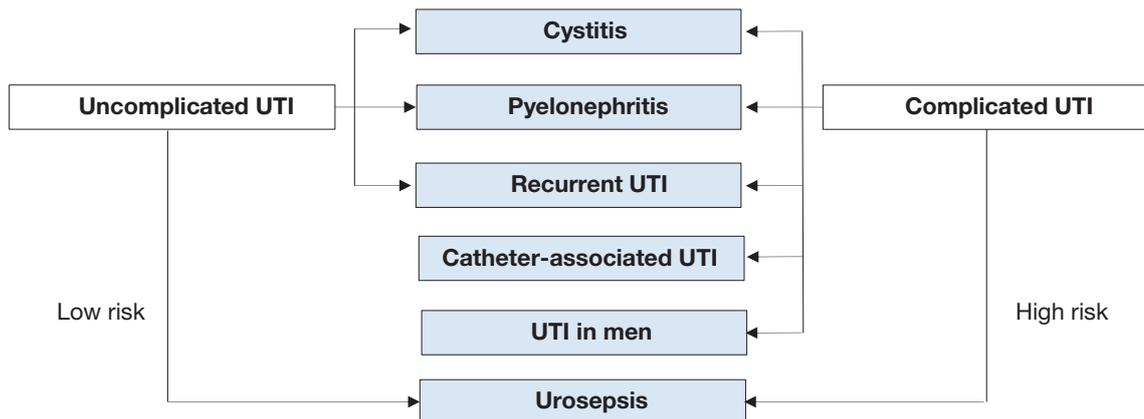
This document was subject to independent peer review prior to publication in 2015 and 2016.

3. THE GUIDELINE

3.1 Classification

Different classification systems of UTI exist. Most widely used are those developed by the Centers for Disease Control and Prevention (CDC) [6], Infectious Diseases Society of America (IDSA) [7], European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [8] as well as the U.S. Food and Drug Administration (FDA) [9, 10]. Current UTI guidelines frequently use the concept of uncomplicated and complicated UTI with a number of modifications (Figure 1). In 2011 the EAU/EAU Section of Infections in Urology proposed the ORENUC classification system based on the clinical presentation of the UTI, categorisation of risk factors and availability of appropriate antimicrobial therapy [11].

Figure 1 – Concept of uncomplicated and complicated UTI



The following classification of UTIs is adopted in the EAU Urological Infections Guidelines:

Classification of UTI	
Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant, pre-menopausal women with no known anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes.
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.
Catheter-associated UTIs	Catheter-associated urinary tract infection (CA-UTI) refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours.
Urosepsis	A systemic, deleterious host response to infection originating from the urinary tract and/or male genital organs. Urosepsis is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia.

3.2 Antimicrobial stewardship

Antimicrobial stewardship programmes aim to optimise the outcome of prevention and treatment of infection whilst curbing overuse and misuse of antimicrobial agents [12-16]. Measures of success include regulating antimicrobial prescribing, and reduction in both the rate of healthcare associated infections such as *Clostridium difficile* and the emergence of resistant organisms [16]. In urology, antimicrobial stewardship programmes should include a series of measures to ensure rational, evidence based use of antimicrobials in the prevention and treatment of infections of the urinary tract and male accessory glands, as well as non-antimicrobial strategies. Programmes require a stewardship team approach comprising urologists, infectious diseases

physicians, microbiologists and clinical pharmacologists or pharmacists [13-16].

The most important components of antimicrobial stewardship programmes are [14]:

- regular training of staff in best use of antimicrobial agents;
- adherence to local, national or international guidelines;
- regular ward visits and consultation with infectious diseases physicians, with audit;
- treatment outcome evaluation;
- monitoring and regular feedback to prescribers of their antimicrobial prescribing performance and local pathogen resistance profiles.

Several studies in hospital settings have shown that regular ward visits and audit of practice by infectious disease physicians markedly reduce overall use of antimicrobial agents by promoting shorter duration of therapy, earlier step-down to oral medication and avoidance of antimicrobial use when patient outcome is unlikely to be compromised [16, 17]. Studies specific to the urology setting are lacking but a case-control study showed reduction in antimicrobial usage and bacterial resistance in hospitalised urology patients when EAU Guidelines on peri-operative prophylaxis were adhered to, without change in the rate of infectious complications [18].

3.3 Asymptomatic bacteriuria in adults

3.3.1 Evidence question

What is the most effective management for people with asymptomatic bacteriuria?

3.3.2 Background

Urinary growth of bacteria in an asymptomatic individual, asymptomatic bacteriuria (ABU), is common, and relates to commensal colonisation [19]. Clinical studies have shown that ABU may protect against superinfecting symptomatic UTI, therefore, treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting for antimicrobial resistance and eradicating a potentially protective ABU strain [20, 21]. The aim of this section is to support the clinician in deciding when ABU should or should not be treated.

3.3.3 Epidemiology, aetiology and pathophysiology

Asymptomatic bacteriuria occurs in an estimated 1-5% of healthy pre-menopausal females, increasing to 4-19% in otherwise healthy elderly females and men, 0.7-27% in patients with diabetes, 2-10% in pregnant women, 15-50% in institutionalised elderly populations, and 23-89% in patients with spinal cord injuries [22]. Asymptomatic bacteriuria in younger men is uncommon, but when detected, chronic bacterial prostatitis must be considered. The spectrum of bacteria in ABU is similar to species found in uncomplicated or complicated UTIs, depending on the presence of risk factors (see sections 3.4 and 3.7).

3.3.4 Diagnostic evaluation

Asymptomatic bacteriuria in an individual without urinary tract symptoms is defined by a mid-stream sample of urine (MSU), showing bacterial growth $\geq 10^5$ cfu/mL, in two consecutive samples in women [23] and in a single sample in men [24]. In a single catheterised sample bacterial growth may be as low as 10^2 cfu/mL to be considered representing true bacteriuria in both men and women [22, 25]. Diagnostic work-up should include measurement of residual urine. Cystoscopy and/or imaging of the upper urinary tract is not mandatory if the patient's medical history is otherwise without remark. If persistent growth of urease producing bacteria, *i.e.* *Proteus mirabilis* is detected, stone formation in the urinary tract must be excluded [26]. In men, a digital rectal examination (DRE) has to be performed to rule out prostate diseases (see section 3.11).

3.3.5 Evidence summary

A systematic search of the literature from January 2000 to September 2016 identified 2,853 titles of which 218 titles were selected for full text review, 61 of these texts were included in the final review [21, 27-83]. For the subgroups of pregnancy, patients scheduled for urologic surgeries, post-menopausal women and institutionalised elderly patients only data from randomised-controlled trials (RCT) was included, on which a meta-analysis was performed. For the remaining subgroups non-RCTs were also included in a narrative synthesis of the evidence. The following patient populations were not covered by the systematic review: immuno-compromised patients, patients with candiduria, dysfunctional and/or reconstructed lower urinary tracts and patients with indwelling catheters.

3.3.6 **Disease management**

3.3.6.1 *Patients without identified risk factors*

Asymptomatic bacteriuria does not cause renal disease or damage [84]. Only one prospective, non-randomised study investigated the effect of treatment of ABU in adult, non-diabetic, non-pregnant women [61], and found no difference in the rate of symptomatic UTIs. Furthermore, as the treatment of ABU has been proven to be unnecessary in high-risk patient subgroups, there is panel consensus that the results of these subgroups can also be applied to patients without identified risk factors. Therefore, screening and treatment of ABU is not recommended in patients without risk factors.

3.3.6.2 *Patients with ABU and recurrent UTI, otherwise healthy*

One RCT investigated the effect of ABU treatment in female patients with recurrent symptomatic UTI and without identified risk factors [21] and demonstrated that treatment of ABU increases the risk of a subsequent symptomatic UTI episode, as compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; 673 patients). This protective effect of spontaneously developed ABU can be used as part of prevention in female patients with recurrent symptomatic UTI. Therefore, treatment of ABU is not recommended. However, occasionally the eradication of a strain considered the causative agent of recurrent episodes of UTI, may be justified. In men with recurrent symptomatic UTI and ABU, chronic bacterial prostatitis must be considered and, if diagnosed, treated (see chapter 3.11).

3.3.6.3 *Pregnant women*

3.3.6.3.1 *Is treatment of ABU beneficial in pregnant women?*

Twelve RCTs comparing antimicrobial treatment of ABU with placebo controls or no treatment [27, 29, 38, 39, 42, 44, 45, 48, 50, 54, 55, 57], with different antibiotic doses and regimens were identified. Eleven RCTs (n=2,002) reported on the rate of symptomatic UTIs [27, 29, 33, 38, 42, 44, 45, 48, 50, 54, 55]. Antibiotic treatment significantly reduced the number of symptomatic UTIs compared to placebo or no treatment (average (RR) 0.20, 95% CI 0.10 to 0.39).

Six RCTs reported on the resolution of bacteriuria [38, 39, 42, 44, 50, 55]. Antibiotic treatment was effective in the resolution of bacteriuria compared to placebo (average RR 2.99, 95% CI 1.65 to 5.39; n=716). Eight RCTs reported on the rate of low birthweights [27, 33, 38, 42, 44, 45, 54, 57]. Antibiotic treatment was associated with lower rates of low birthweight compared to placebo or no treatment (average RR 0.58, 95% CI 0.36 to 0.94; n=1,689). Four RCTs reported on the rate of pre-term deliveries [33, 54, 55, 57]. Antibiotic treatment was associated with lower rate of pre-term delivery compared to placebo or no treatment (average RR 0.34, 95% CI 0.18 to 0.66; n=854).

Based on the beneficial maternal and fetal effects of antibiotic treatment pregnant women should be screened and treated for ABU. However, the panel would like to emphasise that most available studies have low methodological quality and are from the 60's to 80's. Diagnostic and treatment protocols and accessibility to medical services has dramatically changed since then; therefore, the quality of evidence for this recommendation is low. In newer studies of higher methodological quality the beneficial effects of antibiotic treatment are not as evident [33]. Therefore, it is advisable to also consult national recommendations for the treatment of ABU in pregnant women.

3.3.6.3.2 *Which treatment duration should be applied to treat ABU in pregnancy?*

Sixteen RCTs comparing the efficacy of different antibiotic treatments in pregnant women with ABU were identified [28, 32, 34-37, 40, 41, 43, 46, 47, 49, 51-53, 56]. There was significant heterogeneity amongst the studies. Studies compared different antibiotic regimens or the same antibiotic regimens with different durations. The duration of treatment ranged from single dose to continuous treatment (until delivery). For practical purposes the grouping strategy used by the previously published Cochrane Review by Widmer et. al., was adopted with some modifications [85]. The following treatment groups were used for comparison:

1. single dose (single day);
2. short course (2-7 days);
3. long course (8-14 days);
4. continuous (until delivery).

Nine studies compared single dose to short course treatment [28, 34, 35, 40, 41, 46, 47, 49, 53], one study compared single dose to long course treatment [52] and one study compared long course to continuous treatment [56]. As long term and continuous antibiotic treatment is not used in current practice, only studies comparing single dose to standard short course treatment are presented.

3.3.6.3.2.1 Single dose vs. short course treatment

Three RCTs reported on the rate of symptomatic UTIs [34, 40, 46], with no significant difference between the two durations (average RR 1.00, 95% CI 0.58 to 1.71; n=891). Nine RCTs reported on the rate of ABU resolution [28, 34, 35, 40, 41, 46, 47, 49, 53], with no significant difference between the two durations (average RR 0.95, 95% CI 0.90 to 1.01; 1268 women). Six RCTs reported on the rate of side effects [34, 35, 40, 41, 49, 53]. Single dose treatment was associated with significantly less side effects compared to short course treatment (average RR 0.34, 95% CI 0.19 to 0.62; 458 women). Three RCTs reported on the rate of pre-term deliveries [34, 46, 51], with no significant difference between the two durations (average RR 1.15, 95% CI 0.75 to 1.76; 814 women). One RCT reported on the rate of low birthweights [46]. There were significantly more babies with low birthweight in the single dose regimen compared to short course treatment (average RR 1.65, 95% CI 1.06 to 2.57; 714 women).

According to the data analysis, single dose treatment was associated with a significantly lower rate of side effects but a significantly higher rate of low birthweight. Therefore, standard short course treatment should be applied to treat ABU in pregnancy, however it should be emphasised that the overall quality of the scientific evidence backing this recommendation is low.

3.3.6.4 Patients with identified risk-factors

3.3.6.4.1 Diabetes mellitus

Diabetes mellitus, even when well regulated, is reported to correlate to a higher frequency of ABU [86]. One RCT demonstrated that eradicating ABU did not reduce the risk of symptomatic UTI and infectious complications in patients with diabetes mellitus. The time to first symptomatic episode was also similar in both groups. Furthermore, untreated ABU did not correlate to diabetic nephropathy [87]. Screening and treatment of ABU in well-regulated diabetes mellitus is therefore not recommended. However, poorly regulated diabetes is a risk factor for symptomatic UTI and infectious complications.

3.3.6.4.2 ABU in post-menopausal women

Elderly women have an increased incidence of ABU [88]. Four RCTs compared antibiotic treatment of ABU with placebo controls or no treatment, in a post-menopausal female population, with different antibiotic doses and regimens [65-67, 70]. Women in these studies were mostly nursing home residents, which may bias the results of this analysis. Three RCTs reported on the rate of symptomatic UTIs (average RR 0.71, 95% CI 0.49 to 1.05; 208 women) and the resolution of bacteriuria (average RR 1.28, 95% CI 0.50 to 3.24; 203 women) [34, 40, 46], with no significant benefit of antibiotic treatment. Therefore, ABU in post-menopausal women does not require treatment, and should be managed as for pre-menopausal women.

3.3.6.4.3 Elderly institutionalised patients

The rate of ABU is 15-50% in elderly institutionalised patients [89]. Differential diagnosis of ABU from symptomatic UTI is difficult in the multi-diseased and mentally deteriorated patient, and is probably a cause of unnecessary antibiotic treatment [90, 91]. Seven RCTs compared antibiotic treatment of ABU with placebo controls or no treatment in elderly patients, with different antibiotic doses and regimens [63, 65-67, 70, 72, 73].

Three RCTs reported on the rate of symptomatic UTIs [63, 65, 67]. Antibiotic treatment was not significantly beneficial in reducing the rate of symptomatic UTIs compared to placebo or no treatment (average RR 0.68, 95% CI 0.46 to 1.00; 210 patients). Six RCTs reported on the resolution of bacteriuria [63, 65, 67, 70, 72, 73]. There was no benefit of antibiotic treatment compared to placebo in the resolution of ABU (average RR 1.33, 95% CI 0.63 to 2.79; 328 patients). One RCT compared the rates of incontinence in this patient group before and after the eradication of ABU, and found no effect of antibiotic treatment [71]. Therefore, screening and treatment of ABU is not recommended in this patient group.

3.3.6.4.4 Patients with renal transplants

One RCT, one prospective non-randomised and two retrospective studies compared the effect of antibiotic treatment to no treatment in renal transplant patients [74-76, 80]. None of the studies found antibiotic treatment beneficial in terms of reducing the rate of ABU or symptomatic UTIs. Furthermore, there were no significant differences in the rate of graft loss or change in renal function during long-term follow-up [74-76, 80]. Therefore, treatment of ABU is not recommended in renal transplant recipients.

3.3.6.4.5 Patients with dysfunctional and/or reconstructed lower urinary tracts

Patients with lower urinary tract dysfunction (LUTD) (e.g. neurogenic bladder patients secondary to multiple sclerosis, spinal cord injury patients, patients with incomplete bladder emptying, patients with neo-bladder and ileo-cystoplasty, patients using clean intermittent catheterisation (CIC), and patients with ileal conduits, orthotopic bladder replacement and continent reservoirs) frequently become colonised [92, 93]. Studies have shown no benefit in ABU treatment in these patient groups [92, 94]. Furthermore, in LUTD patients who do not

spontaneously develop ABU, deliberate colonisation with an ABU strain (*Escherichia coli* 83972) has shown a protective effect against symptomatic recurrences [95, 96]. Screening and treatment of ABU in these patient groups is therefore, not recommended. If these patient groups develop recurrent symptomatic UTI (see section 3.5) the potential protective effect of a spontaneously developed ABU against lower UTI must be considered before any treatment.

3.3.6.4.6 Patients with catheters in the urinary tract

Patients with indwelling or suprapubic catheters, and nephrostomy tubes, invariably become carriers of ABU, with antibiotic treatment showing no benefit. This is also applicable for patients with ABU and indwelling ureteral stents [97]. Routine treatment of catheter associated bacteriuria is not recommended. For detailed recommendations see section 3.8.

3.3.6.4.7 Patients with ABU subjected to catheter placements/exchanges

In patients subjected to uncomplicated placement/exchanges of indwelling catheters ABU is not considered a risk factor in itself, and should not be screened or treated [98]. In patients subjected to placement/exchanges of nephrostomy tubes and indwelling ureteral stents, ABU is considered a risk factor for infectious complications [99]. Therefore, screening and treatment prior to the procedure is recommended.

3.3.6.4.8 Immuno-compromised and severely diseased patients, patients with candiduria

These patient groups have to be considered individually and the benefit of screening and treatment of ABU should be reviewed in each case. Patients with asymptomatic candiduria may, but not necessarily, have an underlying disorder or defect. Treatment of asymptomatic candiduria is not recommended in patients with an otherwise uncomplicated medical history [100].

3.3.6.5 *Prior to urological surgery*

In diagnostic and therapeutic procedures not entering the urinary tract, ABU is generally not considered as a risk factor, and screening and treatment are not considered necessary. On the other hand, in procedures entering the urinary tract and breaching the mucosa, particularly in endoscopic urological surgery, bacteriuria is a definite risk factor.

Two RCTs [78, 81] and two prospective non-randomised studies [82, 83] compared the effect of antibiotic treatment to no treatment prior to transurethral prostate or bladder tumour resection. Antibiotic treatment significantly reduced the number of post-operative symptomatic UTIs compared to no treatment in the meta-analysis of the two RCTs (average RR 0.19, 95% CI 0.05 to 0.82; 167 patients). The rates of post-operative fever and septicaemia were also significantly lower in case of antibiotic treatment compared to no treatment in the two RCTs.

A urine culture must therefore be taken prior to such interventions and in case of ABU, pre-operative treatment should be given. The recommendations for antibiotic prophylaxis in different urological procedures are given in section 3.15.

3.3.6.6 *Prior to orthopaedic surgery*

One RCT and one multicentre cohort study comparing the treatment of ABU with no treatment prior to orthopaedic surgery (hip arthroplasty/hemiarthroplasty or total knee arthroplasty) were identified [101, 102]. None of the studies showed a beneficial effect of antibiotic treatment in terms of prosthetic joint infection. One study measured the rate of post-operative symptomatic UTIs and found no significant difference between antibiotic treatment and no treatment [102]. Therefore, treatment of bacteriuria is not recommended prior to arthroplasty surgery.

3.3.6.7 *Pharmacological management*

If the decision is taken to eradicate ABU, the same choice of antibiotics and treatment duration as in symptomatic uncomplicated (section 3.4.4.4) or complicated (section 3.7.5) UTI could be given, depending on gender, medical background and presence of complicating factors. Treatment should be tailored and not empirical. Based on clinical experience, if ABU patients complain of odour and mild dysuria, methenamine hippurate 1 g two to three times daily, and/or increased water intake, may be considered.

3.3.7 **Follow-up**

There are no studies focusing on follow-up after treatment of ABU. However, if the resolution of ABU has a clinical significance (e.g. in pregnancy), follow-up with subsequent urine culture is needed to secure the treatment effect.

3.3.8 Recommendations for the management of ABU

Recommendations	LE	GR
Do not screen or treat asymptomatic bacteriuria in the following conditions:		
• women without risk factors;	2a	A*
• patients with well-regulated diabetes mellitus;	1b	A
• post-menopausal women;	1a	A
• elderly institutionalised patients;	1a	A
• patients with dysfunctional and/or reconstructed lower urinary tracts;	2b	B
• patients with catheters in the urinary tract;	4	C
• patients with renal transplants;	1b	A
• patients prior to arthroplasty surgeries;	1b	A
• patients with recurrent urinary tract infections.	1b	A
Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.	1a	A
Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.	1a	A
Take a urine culture following treatment of asymptomatic bacteriuria to secure treatment effect.	4	C

* Upgraded based on panel consensus

3.4 Uncomplicated cystitis

3.4.1 Introduction

Uncomplicated cystitis is defined as acute, sporadic or recurrent cystitis limited to non-pregnant, pre-menopausal women with no known anatomical and functional abnormalities within the urinary tract or comorbidities.

3.4.2 Epidemiology, aetiology and pathophysiology

Almost half of all women will experience at least one episode of cystitis during their lifetime. Nearly one in three women will have had at least one episode of cystitis by the age of 24 years [103]. Risk factors include sexual intercourse, use of spermicide, a new sexual partner, a mother with a history of UTI and a history of UTI during childhood. The spectrum of aetiological agents is similar in uncomplicated cystitis and pyelonephritis, with *E. coli* being the causative pathogen in 70–95% of cases and *Staphylococcus saprophyticus* in 5–10%. Occasionally, other Enterobacteriaceae, such as *P. mirabilis* and *Klebsiella spp.*, are isolated [104].

3.4.3 Diagnostic evaluation

3.4.3.1 Clinical diagnosis

The diagnosis of uncomplicated cystitis can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge or irritation [105, 106]. In elderly women genitourinary symptoms are not necessarily related to cystitis [107].

3.4.3.2 Differential diagnosis

Uncomplicated cystitis should be differentiated from ABU, which is considered not to be infection but rather a commensal colonisation, which should not be treated and therefore not screened for, except if it is considered a risk factor in clearly defined situations see section 3.3.

3.4.3.3 Laboratory diagnosis

Urine dipstick testing is a reasonable alternative to culture for diagnosis of uncomplicated cystitis [108, 109]. Urine cultures are recommended in the following situations:

- suspected acute pyelonephritis;
- symptoms that do not resolve or recur within two to four weeks after the completion of treatment;
- women who present with atypical symptoms [110, 111];
- pregnant women;
- males with suspected UTI.

A colony count of 10^3 cfu/mL of uropathogens is microbiologically diagnostic in women who present with symptoms of uncomplicated cystitis [112]. Women who present with atypical symptoms of either uncomplicated cystitis or uncomplicated pyelonephritis, as well as those who fail to respond to appropriate antimicrobial therapy should be considered for additional diagnostic studies.

3.4.3.4 Recommendations for the diagnostic evaluation of uncomplicated cystitis

Recommendations	LE	GR
Diagnose uncomplicated cystitis based on: <ul style="list-style-type: none"> a focused history of lower urinary tract symptoms (dysuria, frequency and urgency); the absence of vaginal discharge or irritation, in women who have no other risk factors for complicated urinary tract infections. 	2a	B
Use urine dipstick testing, as an alternative to culture for diagnosis of acute uncomplicated cystitis.	2a	B
Urine cultures should be done in the following situations: <ul style="list-style-type: none"> suspected acute pyelonephritis; symptoms that do not resolve or recur within two-four weeks after the completion of treatment; women who present with atypical symptoms; pregnant women. 	4	B*

* Upgraded based on panel consensus

3.4.4 Disease management

Antimicrobial therapy is recommended because clinical success is significantly more likely in women treated with antimicrobials compared with placebo [113]. The choice of antimicrobial therapy should be guided by [105]:

- spectrum and susceptibility patterns of the aetiological pathogens;
- efficacy for the particular indication in clinical studies;
- tolerability and adverse reactions;
- adverse ecological effects;
- costs;
- availability.

According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg three times a day for three to five days, and nitrofurantoin macrocrystal 100 mg twice daily for 5 days, are considered as drugs of first choice, when available [114-116].

Alternative antimicrobials include trimethoprim alone or combined with a sulphonamide. Co-trimoxazole (160/800 mg twice daily of three days) or trimethoprim (200 mg twice daily for five days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20% [117, 118]. Despite lower resistance rates in certain countries, fluoroquinolones are not considered first choice because of adverse effects including negative ecological effects and selection for resistance.

Aminopenicillins are no longer suitable for empirical therapy because of worldwide high *E. coli* resistance. Aminopenicillins in combination with a beta-lactamase inhibitor such as ampicillin/sulbactam or amoxicillin/clavulanic acid and oral cephalosporins are in general not effective as short-term therapy and are not recommended for empirical therapy due to ecological collateral damage, but may be used in selected cases [119, 120].

3.4.4.1 Cystitis in pregnancy

Short courses of antimicrobial therapy can also be considered for treatment of cystitis in pregnancy [121], but not all antimicrobials are suitable during pregnancy. In general penicillins, cephalosporins, fosfomycin, nitrofurantoin (not in case of glucose-6-phosphate dehydrogenase deficiency and during the end of pregnancy), trimethoprim (not in the first trimester) and sulphonamides (not in the last trimester), can be considered.

3.4.4.2 Cystitis in men

Uncomplicated cystitis without involvement of the prostate is uncommon, and therefore treatment with antimicrobials penetrating into the prostate tissue is needed in males with symptoms of UTI. A treatment duration of at least seven days is recommended, preferably with trimethoprim sulphamethoxazole or a fluoroquinolone if in accordance with susceptibility testing (see section 3.4.4.4) [122].

3.4.4.3 Renal insufficiency

In patients with renal insufficiency the choice of antimicrobials may be influenced by decreased renal excretion. However, most antimicrobials, have a wide therapeutic index. No adjustment of dose is necessary until glomerular filtration rate (GFR) is < 20 mL/min, except for antimicrobials with nephrotoxic potential, e.g. aminoglycosides. Combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic. Nitrofurantoin and tetracyclines are contraindicated, but not doxycycline [122].

3.4.4.4 Recommendations for antimicrobial therapy for uncomplicated cystitis

Recommendations					
Antimicrobial	Daily dose	Duration of therapy	Comments	LE	GR
First choice					
Fosfomycin trometamol	3 g SD	1 day	Recommended in women not men.	1	A
Nitrofurantoin macrocrystal	100 mg b.i.d	5 days			
Pivmecillinam	400 mg t.i.d	3-5 days			
Alternatives					
Cephalosporins (e.g. cefadroxil)	500 mg b.i.d	3 days	Or comparable.	1b	B
If the local resistance pattern for <i>E. coli</i> is < 20%					
Trimethoprim	200 mg b.i.d	5 days	Not in the first trimenon of pregnancy.	1b	B
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	3 days	Not in the last trimenon of pregnancy.		
Treatment in men					
Trimethoprim-sulphamethoxazole	160/800 mg b.i.d	7 days	Restricted to men, fluoroquinolones can also be prescribed in accordance with local susceptibility testing.	4	C

SD = single dose; b.i.d = twice daily; t.i.d = three times daily.

3.4.5 Follow-up

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated [123]. In women whose symptoms do not resolve by end of treatment, and in those whose symptoms resolve but recur within two weeks, urine culture and antimicrobial susceptibility testing should be performed [124]. For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a seven day regimen using another agent should be considered [124].

3.5 Recurrent UTIs

3.5.1 Introduction

Recurrent UTIs (rUTIs) are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months. Although rUTIs include both lower tract infection (cystitis) and upper tract infection (pyelonephritis), repeated pyelonephritis should prompt consideration of a complicated aetiology.

3.5.2 Diagnostic evaluation

Recurrent UTIs are common. Risk factors are outlined in Table 1. Diagnosis of rUTI should be confirmed by urine culture. An extensive routine workup including cystoscopy, imaging, etc. is not routinely recommended as the diagnostic yield is low [125]. However, it should be performed without delay in atypical cases, for example, if renal calculi or outflow obstruction is suspected.

Table 1: Age-related risk factors for rUTI in women [89, 107, 126]

Young and pre-menopausal women	Post-menopausal and elderly women
Sexual intercourse	History of UTI before menopause
Use of spermicide	Urinary incontinence
A new sexual partner	Atrophic vaginitis due to oestrogen deficiency
A mother with a history of UTI	Cystocele
History of UTI during childhood	Increased post-void urine volume
Blood group antigen secretory status	Blood group antigen secretory status
	Urine catheterisation and functional status
	deterioration in elderly institutionalised women

3.5.3 **Disease management and follow-up**

Prevention of rUTIs includes counselling regarding avoidance of risk factors, non-antimicrobial measures and antimicrobial prophylaxis [124]. These interventions should be attempted in this order. Any urological risk factors must be identified and treated. Significant residual urine should be treated optimally, including by clean intermittent catheterisation when judged to be appropriate.

3.5.3.1 *Behavioural modifications*

A number of behavioural and personal hygiene measures (e.g. reduced fluid intake, habitual and post-coital delayed urination, wiping from back to front after defecation, douching and wearing occlusive underwear) have been suggested to decrease the risk of rUTI. However, studies that have explored these risk factors have consistently documented the lack of association with rUTI [124].

3.5.3.2 *Non-antimicrobial prophylaxis*

There are many non-antimicrobial measures recommended for rUTIs but only a few are supported by well-designed studies [127, 128].

3.5.3.2.1 Hormonal replacement

In post-menopausal women vaginal oestrogen replacement, but not oral oestrogen, showed a trend towards preventing rUTI [127, 129].

3.5.3.2.2 Immunoactive prophylaxis

OM-89 (Uro-Vaxom®) is sufficiently well documented and has been shown to be more effective than placebo in several randomised trials with a good safety profile. Therefore, it can be recommended for immunoprophylaxis in female patients with rUTIs [127, 130-132]. Efficacy in other groups of patients and relative to antimicrobial prophylaxis remains to be established.

The vaginal vaccine Urovac® slightly reduced rUTIs. Primary immunisation followed by booster immunisation increased time to re-infection [127].

3.5.3.2.3 Prophylaxis with probiotics (*Lactobacillus* spp.)

Pooled data from a recent meta-analysis shows no convincing benefit of lactobacillus products as prophylaxis for rUTI [133]. However, differences in effectiveness between available preparations suggest further trials are needed before any definitive recommendation for or against their use can be made.

3.5.3.2.4 Prophylaxis with cranberry

Limited studies have suggested that cranberry is useful in reducing the rate of lower UTIs in women [134, 135]. However, a meta-analysis including 24 studies and comprising 4,473 participants showed that cranberry products did not significantly reduce the occurrence of symptomatic UTI for women with rUTI [136]. Due to these contradictory results, no recommendation on the daily consumption of cranberry products can be made.

3.5.3.2.5 Prophylaxis with D-mannose

In a randomised placebo-controlled non-blinded clinical trial, it was shown that a daily dose of 2 g D-mannose was significantly superior to placebo and as effective as 50 mg nitrofurantoin in preventing rUTI [137]. This is indicative but not sufficient for a recommendation therefore, D-mannose should at present only be used within the context of clinical investigations.

3.5.3.2.6 Endovesical instillation

Endovesical instillation of hyaluronic acid and chondroitin sulphate have been used for glycosaminoglycan

(GAG) layer replenishment in the therapy of interstitial cystitis, overactive bladder, radiation cystitis, and for prevention of rUTI [138]. A recent review of 27 clinical studies concluded that large-scale trials are urgently needed to assess the benefit of this type of therapy [139]. Therefore, no general recommendation is possible at this stage.

3.5.3.3 Antimicrobials for preventing rUTI

3.5.3.3.1 Continuous low-dose antimicrobial prophylaxis and post-coital prophylaxis

Antimicrobials may be given as continuous low-dose prophylaxis for longer periods (three to six months), or as post-coital prophylaxis, as both regimens reduce the rate of rUTI [140]. It is mandatory to offer both options after counselling, and when behavioural modifications and non-antimicrobial measures have been unsuccessful. Regimens include nitrofurantoin 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every ten days, and during pregnancy cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily [124]. Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI [141].

3.5.3.3.2 Self-diagnosis and self-treatment

In patients with good compliance, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered [142]. The choice of antimicrobials is the same as for sporadic acute uncomplicated UTI (section 3.4.4.4).

3.5.4 Recommendations for the diagnostic evaluation and treatment of rUTIs

Recommendations	LE	GR
Do not perform an extensive routine workup in women with recurrent UTI without risk factors.	1b	B
Advise patients on behavioural modifications which might reduce the risk of recurrent UTI.	3	C
Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI.	1b	A
Use immunoactive prophylaxis to reduce recurrent UTI in all age groups.	1a	A
When non-antimicrobial interventions have failed, continuous or post-coital antimicrobial prophylaxis should be used to prevent recurrent UTI, but patients should be counselled regarding possible side effects.	2b	B
For patients with good compliance, self-administrated short term antimicrobial therapy should be considered.	2b	A*

* Upgraded based on panel consensus.

3.6 Uncomplicated pyelonephritis

Uncomplicated pyelonephritis is defined as pyelonephritis limited to non-pregnant, pre-menopausal women with no known urological abnormalities or comorbidities.

3.6.1 Diagnostic evaluation

3.6.1.1 Clinical diagnosis

Pyelonephritis is suggested by fever (> 38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, with or without the typical symptoms of cystitis [143]. Pregnant women with acute pyelonephritis need special attention, as this kind of infection may have not only an adverse effect on the mother with anaemia, renal and respiratory insufficiency, but also on the unborn child with more frequent pre-term labour and birth [144].

3.6.1.2 Differential diagnosis.

It is vital to differentiate as soon as possible between uncomplicated and complicated mostly obstructive pyelonephritis, as the latter can rapidly lead to urosepsis. This differential diagnosis should be made by the appropriate imaging technique (see section 3.6.1.4).

3.6.1.3 Laboratory diagnosis

Urinalysis including the assessment of white and red blood cells and nitrite, is recommended for routine diagnosis [145]. In addition, urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis.

3.6.1.4 Imaging diagnosis

Evaluation of the upper urinary tract with ultrasound (US) should be performed to rule out urinary obstruction or renal stone disease [146]. Additional investigations, such as an unenhanced helical computed tomography

(CT), excretory urography, or dimercaptosuccinic acid (DMSA) scanning, should be considered if the patient remains febrile after 72 hours of treatment [146]. For diagnosis of complicating factors in pregnant women, US or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus [146].

3.6.2 **Recommendations for the diagnostic evaluation of uncomplicated pyelonephritis**

Recommendations	LE	GR
Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	4	A*
Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.	4	A*
Perform ultrasound of the upper urinary tract to exclude obstructive pyelonephritis.	4	A*
Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.	4	A*

*Upgraded based on panel consensus.

3.6.3 **Disease management**

3.6.3.1 **Outpatient treatment**

Fluoroquinolones and cephalosporines are the only microbial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis. However, oral cephalosporines achieve significantly lower concentrations than intravenous cephalosporines. Local fluoroquinolone resistance should be < 10%. Other agents such as nitrofurantoin, fosfomycin, and pivmecillinam should be avoided because these agents do not achieve adequate renal tissue levels [147]. In the setting of fluoroquinolone hypersensitivity or known resistance, other acceptable choices include trimethoprim-sulfamethoxazole (160/800 mg) or an oral beta-lactam, if the uropathogen is known to be susceptible. If such agents are used in the absence of antimicrobial susceptibility results, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.

3.6.3.2 **Inpatient treatment**

Patients with uncomplicated pyelonephritis requiring hospitalisation should be treated initially with an intravenous antimicrobial regimen such as a fluoroquinolone, an aminoglycoside (with or without ampicillin), an extended-spectrum cephalosporin, an extended-spectrum penicillin, or a carbapenem [148]. The choice between these agents should be based on local resistance patterns and optimised on the basis of drug susceptibility results. In patients presenting with signs of urosepsis empiric antimicrobial coverage for extended-spectrum beta-lactamases (ESBL)-producing organisms is warranted [149]. Patients initially treated with parenteral therapy who improve clinically and can tolerate oral fluids may transition to oral antimicrobial therapy [150].

3.6.3.2.1 Recommendations for empirical oral antimicrobial therapy in uncomplicated pyelonephritis

Recommendations					
Antimicrobial	Daily dose	Duration of therapy	LE	GR	Comments
Ciprofloxacin	500-750 mg b.i.d	7-10 days	1b	B	Fluoroquinolone resistance should be less than 10 percent.
Levofloxacin	750 mg q.d	5 days	1b	B	
Trimethoprim sulphamethoxazol	160/800 mg b.i.d	7-14 days	1b	B	If such agents are used empirically, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.
Cefpodoxime	200 mg b.i.d	10 days	4	B*	
Ceftibuten	400 mg q.d	10 days	4	B*	

*Upgraded based on panel consensus.

b.i.d = twice daily; q.d = every day.

3.6.3.2.2 Recommendations for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis

Recommendations				
Antimicrobials	Daily dose	LE	GR	Comments
Ciprofloxacin	400 mg b.i.d	1b	B	
Levofloxacin	750 mg q.d	1b	B	
Cefotaxime	2 g t.i.d	2	A*	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftazidime	1-2 g t.i.d	2	A*	
Co-amoxiclav	1.5 g t.i.d	2	C	Not studied as monotherapy in acute uncomplicated pyelonephritis. Mainly for Gram-positive pathogens.
Ceftriaxone	1-2 g q.d	1b	A*	Lower dose studied, but higher dose recommended. Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Cefepime	1-2 g b.i.d	1b	B	
Piperacillin/tazobactam	2.5-4.5 g t.i.d	1b	A*	
Ceftolozane/tazobactam	1.5 g t.i.d	1b	B	
Ceftazidime/avibactam	2.5 g t.i.d	1b	B	
Gentamicin	5 mg/kg q.d	1b	B	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	1b	B	
Ertapenem	1 g q.d	1b	B	Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Imipenem/cilastatin	0.5/0.5 g t.i.d	1b	B	
Meropenem	1 g t.i.d	2	B	
Doripenem	0.5 g t.i.d	1b	B	

* Upgraded based on panel consensus.

b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

In pregnant women with pyelonephritis, outpatient management with appropriate antimicrobials may also be considered, provided symptoms are mild and close follow-up is feasible [151, 152]. In more severe cases of pyelonephritis, hospitalisation and supportive care are usually required. After clinical improvement parenteral therapy can also be switched to oral therapy for a total treatment duration of seven to ten days. In men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected a minimum treatment duration of two weeks is recommended, preferably with a fluoroquinolone since prostatic involvement is frequent [153].

3.6.4 Follow-up

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated, except in pregnant women, if asymptomatic bacteriuria is an issue (see section 3.3.6.3).

3.7 Complicated UTIs

3.7.1 Introduction

A complicated UTI (cUTI) occurs in an individual in whom factors related to the host (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection [154-156]. The underlying factors that are generally accepted to result in a cUTIs are outlined in Table 2. The designation of cUTI encompasses a wide variety of underlying conditions that result in a remarkably heterogeneous patient population. Therefore, it is readily apparent that a universal approach to the evaluation and treatment of cUTIs is not sufficient, although there are general principles of management that can be applied to the majority of patients with cUTIs. The following recommendations are based on the Stichting Werkgroep Antibioticabeleid (SWAB) Guidelines from the Dutch Working Party on Antibiotic Policy [157].

Table 2: Factors associated with complicated UTIs [154-156]

Obstruction at any site in the urinary tract	UTI in males
Foreign body	Pregnancy
Incomplete voiding	Diabetes
Vesicoureteral reflux	Immunosuppression
Recent history of instrumentation	Healthcare-associated infections

3.7.2 **Diagnostic evaluation**

3.7.2.1 *Clinical presentation*

A cUTI is associated with clinical symptoms (e.g. dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever), although in some clinical situations the symptoms may be atypical for example, in neuropathic bladder disturbances or catheter-associated UTI (CA-UTI). Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a post-operative CA-UTI, which might disappear spontaneously as soon as the catheter is removed. Clinicians must also recognise that symptoms, especially lower urinary tract symptoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as, for example, benign prostatic hyperplasia and autonomic dysfunction in patients with spinal lesions and neurogenic bladders. Concomitant medical conditions, such as diabetes mellitus and renal failure, which can be related to urological abnormalities, are often also present in a cUTI.

3.7.2.2 *Urine culture*

Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients suspected of having a cUTI.

3.7.3 **Microbiology (spectrum and antimicrobial resistance)**

A broad range of microorganisms cause cUTIs. The spectrum is much larger than in uncomplicated UTIs and the bacteria are more likely to be resistant (especially in treatment-related cUTI) than those isolated in uncomplicated UTIs [158, 159]. *E. coli*, *Proteus spp.*, *Klebsiella spp.*, *Pseudomonas spp.*, *Serratia spp.* and *Enterococcus spp.* are the most common strains found in cultures. Enterobacteriaceae predominate (60-75%), with *E. coli* as the most common pathogen; particularly if the UTI is a first infection. Otherwise, the bacterial spectrum may vary over time and from one hospital to another [160].

3.7.4 **General principles of cUTI treatment**

Appropriate management of the urological abnormality or the underlying complicating factor is mandatory. Optimal antimicrobial therapy for cUTI depends on the severity of illness at presentation, as well as local resistance patterns and specific host factors (such as allergies). In addition, urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored and followed by (oral) administration of an appropriate antimicrobial agent on the basis of the isolated uropathogen.

3.7.4.1 *Choice of antimicrobials*

In the recently updated IDSA guidelines for the treatment of uncomplicated UTI, it is recommended that the resistance percentages of causative micro-organisms must be < 20% to consider an agent suitable for empirical treatment of a lower UTI and must be < 10% for treatment of an upper UTI. Considering the current resistance percentages of amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole, it can be concluded that these agents are not suitable for the empirical treatment of pyelonephritis in a normal host and, therefore, also not for treatment of all cUTIs [161]. The same applies to ciprofloxacin and other fluoroquinolones in urological patients [161].

Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen, such as an aminoglycoside with or without amoxicillin or a second or third generation cephalosporin or an extended-spectrum penicillin with or without an aminoglycoside [157]. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results [147]. These recommendations are not only suitable for pyelonephritis but for all other cUTIs.

In view of the high degree of resistance, particularly among patients admitted to the department of urology, fluoroquinolones are not automatically suitable as empirical antimicrobial therapy, especially when the patient has used ciprofloxacin in the last six months [162]. Fluoroquinolones can only be recommended as empirical treatment when the patient is not seriously ill and it is considered safe to start initial oral treatment or if the patient has had an anaphylactic reaction to beta-lactam antimicrobials.

3.7.4.2 Duration of antimicrobial therapy

Treatment for seven to fourteen days is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality [7].

3.7.5 Recommendations for the treatment of complicated UTIs.

Recommendations	LE	GR
Do not use amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole for empirical treatment of complicated UTI.	2	A
Use the combination of: <ul style="list-style-type: none"> • amoxicillin plus an aminoglycoside; • a second generation cephalosporin plus an aminoglycoside; • a third generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms. 	2	A
Only use ciprofloxacin provided that the local resistance percentages are < 10% when; <ul style="list-style-type: none"> • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials. 	2	A
Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from the urology department or when patients have used fluoroquinolones in the last six months.	2	A
Use an initial one-time intravenous dose of a long-acting antimicrobial, such as a third generation cephalosporin or an aminoglycoside if the prevalence of fluoroquinolone resistance is thought to be > 10% and resistance data are pending.	2	A
If the prevalence of fluoroquinolone resistance is thought to be > 10% and the patient has contra indications for third generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with uncomplicated pyelonephritis.	2	A
In the event of hypersensitivity to penicillin, a third generation cephalosporin can still be prescribed, with the exception of systemic anaphylaxis in the past.	2	A
In patients with a UTI with systemic symptoms, empirical treatment should cover ESBL in the initial treatment only in patients who are colonised with ESBL-producing micro-organisms. The resistance pattern of the ESBL strain should guide empirical therapy.	2	A

ESBL = Extended-spectrum beta-lactamase.

3.8 Catheter-associated UTIs

3.8.1 Introduction

Catheter-associated UTI refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours. The urinary catheter literature is problematic as many published studies use the term CA-bacteriuria without providing information on what proportion are CA-ABU and CA-UTI, and some studies use the term CA-UTI when referring to CA-ABU or CA-bacteriuria [158]. The following recommendations are based on the Stichting Werkgroep Antibioticabeleid (SWAB) Guidelines from the Dutch Working Party on Antibiotic Policy [157] as well as the IDSA Guidelines [158].

3.8.2 Epidemiology, aetiology and pathophysiology

Catheter-associated UTIs are the leading cause of secondary health care-associated bacteraemia. Approximately 20% of hospital-acquired bacteraemias arise from the urinary tract, and the mortality associated with this condition is approximately 10% [163]. The incidence of bacteriuria associated with indwelling catheterisation is 3-8% per day [164-168]. The duration of catheterisation is presumable the most important risk factor for the development of a CA-UTI [169, 170]. Urinary catheterisation perturbs host defence mechanisms and provides easier access of uropathogens to the bladder. Indwelling urinary catheters facilitate colonisation with uropathogens by providing a surface for the attachment of host cell binding receptors recognised by bacterial adhesins, thus enhancing microbial adhesion. In addition, the uroepithelial mucosa is disrupted, exposing new binding sites for bacterial adhesins, and residual urine in the bladder is increased through pooling below the catheter bulb [171]. Catheter-associated UTIs are often polymicrobial and caused by multiple-drug resistant uropathogens.

3.8.3 Diagnostic evaluation

3.8.3.1 Clinical diagnosis

Signs and symptoms compatible with CA-UTI include new onset or worsening of fever, rigors, altered mental

status, malaise, or lethargy with no other identified cause, flank pain, costovertebral angle tenderness, acute haematuria, pelvic discomfort and in those whose catheters have been removed dysuria, urgent or frequent urination and suprapubic pain or tenderness [157]. In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI [157, 158].

3.8.3.2 *Laboratory diagnosis*

Microbiologically CA-UTI is defined by microbial growth of $\geq 10^3$ cfu/mL of one or more bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours. In catheterised patients, pyuria is not diagnostic for CA-UTI. The presence, absence, or degree of pyuria should not be used to differentiate CA-ABU from CA-UTI. Pyuria accompanying CA-ABU should not be interpreted as an indication for antimicrobial treatment. The absence of pyuria in a symptomatic patient suggests a diagnosis other than CA-UTI [158].

3.8.3.3 *Recommendations for diagnostic evaluation of CA-UTI*

Recommendations	LE	GR
Do not carry out routine urine culture in asymptomatic catheterised patients.	1a	A
Do not use pyuria as an indicator for catheter-associated UTI.	2	A
Do not use the presence, absence, or degree of pyuria to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI.	2	A
Do not use the presence or absence of odorous or cloudy urine alone to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI.	3	C

3.8.4 *Disease management*

A urine specimen for culture should be obtained prior to initiating antimicrobial therapy for presumed CA-UTI due to the wide spectrum of potential infecting organisms and the increased likelihood of antimicrobial resistance. The urine culture should be obtained from the freshly placed catheter prior to the initiation of antimicrobial therapy [158].

Seven days is the recommended duration of antimicrobial treatment for patients with CA-UTI who have prompt resolution of symptoms, and two to fourteen days of treatment is recommended for those with a delayed response, regardless of whether the patient remains catheterised or not [158]. A five-day regimen of levofloxacin may be considered in patients with CA-UTI who are not severely ill. Data are insufficient to make such a recommendation about other fluoroquinolones.

A three-day antimicrobial regimen may be considered for women aged ≤ 65 years who develop CA-UTI without upper urinary tract symptoms after an indwelling catheter has been removed. If an indwelling catheter has been in place for twelve weeks at the onset of CA-UTI and is still indicated, the catheter should be replaced to hasten resolution of symptoms and to reduce the risk of subsequent CA-bacteriuria and CA-UTI. If use of the catheter can be discontinued, a culture of a voided midstream urine specimen should be obtained prior to the initiation of antimicrobial therapy to help guide treatment [158].

3.8.4.1 *Recommendations for disease management and prevention of CA-UTI*

Recommendations	LE	GR
Take a urine culture prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed.	3	A*
Do not treat catheter-associated asymptomatic bacteriuria in general.	1a	A
Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate).	1a	A
Replace or remove the indwelling catheter before starting antimicrobial therapy.	4	B*
Do not apply topical antiseptics or antimicrobials to the catheter, urethra or meatus.	1a	A
Do not use prophylactic antimicrobials to prevent catheter-associated UTIs.	1a	A
The duration of catheterisation should be minimal.	2a	B
Remove an indwelling catheter after non-urological operation within the same day.	1b	B
Change long-term indwelling catheters at intervals adapted to the individual patient.	3	C

* Upgraded based on panel consensus.

3.8.5 *Follow-up*

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated.

3.9 **Urosepsis**

3.9.1 *Introduction*

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a cUTI. Systemic inflammatory response syndrome (SIRS), characterised by fever or hypothermia, hyperleukocytosis or leukopenia, tachycardia and tachypnoea, is recognised as the first event in a cascade leading to multi-organ failure (Figure 2). Mortality is considerably increased the more severe the sepsis is.

The treatment of urosepsis involves adequate life-supporting care, appropriate and prompt antimicrobial therapy, adjunctive measures and the optimal management of urinary tract disorders [172]. The decompression of any obstruction and drainage of larger infectious abscess in the urinary tract is essential as first-line focus control [172]. Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists.

Urosepsis is seen in both community-acquired and healthcare associated infections. Nosocomial urosepsis may be reduced by measures used to prevent nosocomial infection, e.g. reduction of hospital stay, early removal of indwelling urethral catheters, avoidance of unnecessary urethral catheterisation, correct use of closed catheter systems, and attention to simple daily aseptic techniques to avoid cross-infection.

Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia.

3.9.2 *Epidemiology, aetiology and pathophysiology*

Urinary tract infections can manifest from bacteriuria with limited clinical symptoms to sepsis or severe sepsis, depending on localised and potential systemic extension. It is important to note that a patient can move from an almost harmless state to severe sepsis in a very short time.

Mortality rates associated with severe sepsis vary depending on the organ source [173] with urinary tract sepsis generally having a lower mortality than that from other sources [174]. Sepsis is more common in men than in women [175]. In recent years, the overall incidence of sepsis arising from all sources has increased by 8.7% per year [173], but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000) [176]. Although sepsis due to fungal organisms from some sites has increased and Gram-positive bacteria have become the predominant pathogen overall, Gram-negative bacteria remain predominant in urosepsis [177, 178].

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include elderly patients, diabetics, immunosuppressed patients, such as transplant recipients and patients receiving cancer chemotherapy or corticosteroids. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, neurogenic bladder disorders, or endoscopic manoeuvres. However, all patients can be affected by bacterial species that are capable of inducing inflammation within the urinary tract.

3.9.3 *Diagnostic evaluation*

Clinical diagnosis of a UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leukocyturia. Table 3 details the current criteria for the diagnosis of sepsis and septic shock.

Table 3. Definition and criteria of sepsis and septic shock [179-181]

Disorder	Definition
Systematic inflammatory response syndrome (SIRS)	Response to a wide variety of clinical insults, which can be infectious, as in sepsis but may also be non-infectious in aetiology (e.g. burns, or pancreatitis). This systemic response is manifested by two or more of the following criteria: <ul style="list-style-type: none"> • temperature > 38°C or < 36°C; • heart rate > 90 bpm; • respiratory rate > 20 breaths/min or PaCO₂ < 32 mmHg (< 4.3 kPa); • white blood cell count > 12,000 cells/mm³ or < 4,000 cells/mm³ or > 10% immature (band) forms.
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical application, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. For rapid identification a quickSOFA (qSOFA) score was developed: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less.
Septic shock	Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

3.9.4 **Physiology and biochemical markers**

E. coli remains the most prevalent microorganism. In several countries, bacterial strains can be resistant or multi-resistant and therefore difficult to treat [178]. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection.

3.9.4.1 *Cytokines as markers of the septic response*

Cytokines are involved in the pathogenesis of sepsis syndrome [174]. They are molecules that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood [174].

3.9.4.2 *Procalcitonin and mid-regional proadrenomedulline*

Procalcitonin is the inactive pro-peptide of calcitonin. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels rise [182]. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. Mid-regional proadrenomedulline is another sepsis marker. Mid-regional proadrenomedullin has been shown to play a decisive role in the induction of hyperdynamic circulation during the early stages of sepsis and progression to septic shock [183]. Procalcitonin monitoring may be useful in patients likely to develop sepsis and to differentiate from a severe inflammatory status not due to bacterial infection [182, 184]. In addition serum lactate is a marker of organ dysfunction and is associated with mortality in sepsis [185]. Serum lactate should therefore also be monitored in patients with severe infections.

3.9.5 **Disease management**

3.9.5.1 *Prevention*

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Urosepsis treatment requires a combination of treatment including treatment of the cause (obstruction of the urinary tract), adequate life-support care, and appropriate antimicrobial therapy [174]. In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

3.9.5.1.1 Preventive measures of proven or probable efficacy

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections [186, 187] they include:

- Isolation of all patients infected with multi-resistant organisms to avoid cross-infection.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
- Reduction in hospital stay, it is well known that long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
- Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting [188]. Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, including the routine use of protective disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

3.9.5.1.2 Appropriate peri-operative antimicrobial prophylaxis

For appropriate peri-operative antimicrobial prophylaxis see section 3.15. The potential side-effects of antibiotics must be considered before their administration in a prophylactic regimen.

3.9.5.2 *Treatment*

During the first six hours of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following:

- central venous pressure (CVP) 8-12 mmHg;
- mean arterial pressure (MAP) 65-90 mmHg;
- central venous oxygen (CVO₂) > 70%;
- haematocrit (HKT) > 30 %;
- urine output > 0.5 mL/kg/hr.

Early goal-directed resuscitation was initially shown to improve survival for emergency department patients presenting with septic shock in a randomised, controlled, single-centre study [189]. However, recent follow up studies in an improved emergency medicine background have not achieved positive effects with this strategy [190-192].

3.9.5.2.1 Antimicrobial therapy

Initial empiric antimicrobial therapy should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available [172]. The dosage of the antimicrobial substances is of paramount importance in patients with sepsis syndrome and should generally be high, with the exception of patients in renal failure [172]. Antimicrobials must be administered no later than one hour after clinical assumption of sepsis (Figure 2) [172].

3.9.5.2.1.1 Recommendations for parenteral antimicrobial therapy of urosepsis

Recommendations				
Antimicrobials	Daily dose	LE	GR	Comments
Cefotaxime	2 g t.i.d	2	A*	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftazidime	1-2 g t.i.d	2	A*	
Ceftriaxone	1-2 g q.d	1b	A*	Lower dose studied, but higher dose recommended. Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Cefepime	1-2 g b.i.d	1b	B	
Piperacillin/tazobactam	2.5-4.5 g t.i.d	1b	A*	
Ceftolozane/tazobactam	1.5 g t.i.d	1b	B	
Ceftazidime/avibactam	2.5 g t.i.d	1b	B	
Gentamicin	5 mg/kg q.d	1b	B	
Amikacin	15 mg/kg q.d	1b	B	
Ertapenem	1 g q.d	1b	B	Same protocol for acute uncomplicated pyelonephritis and complicated UTI (stratification not always possible).
Imipenem/cilastatin	0.5/0.5 g t.i.d	1b	B	
Meropenem	1 g t.i.d	2	B	
Doripenem	0.5 g t.i.d	1b	B	

* Upgraded based on panel consensus.

b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

3.9.5.2.2 Source control

Drainage of any obstruction in the urinary tract and removal of foreign bodies, such as urinary catheters or stones, should lead to resolution of symptoms and recovery. These are key components of the strategy. This condition is an absolute emergency.

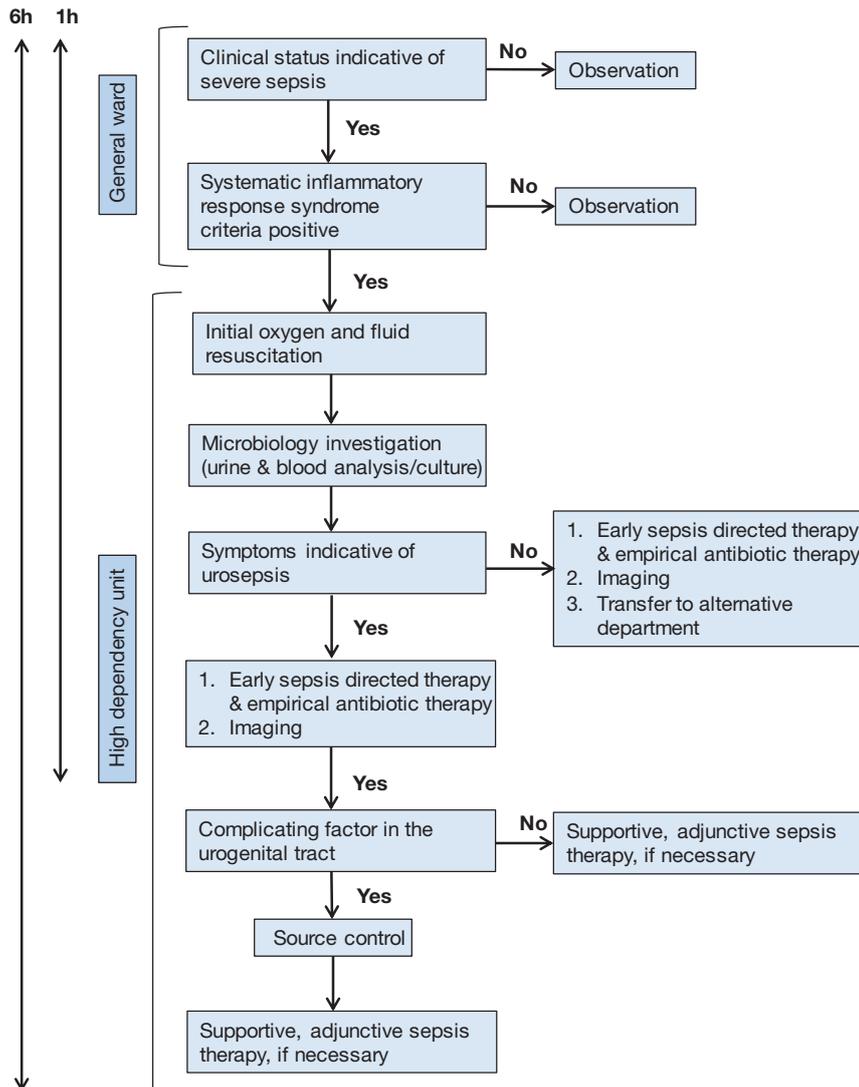
3.9.5.2.3 Adjunctive measures

The most important adjunctive measures in the management of sepsis are the following [172]:

- fluid therapy with crystalloids, or albumin, if crystalloids are not adequately increasing blood pressure;
- as vasopressors norepinephrine should be used primarily, dobutamine in myocardial dysfunction;
- hydrocortisone should be given only if fluid and vasopressors do not achieve a mean arterial pressure of ≥ 65 mmHg;
- blood products should be given to target a haemoglobin level of 7-9 g/dL;
- mechanical ventilation should be applied with a tidal volume 6 ml/kg and plateau pressure ≤ 30 cm H₂O and a high positive end-expiratory pressure;
- sedation should be given minimally, neuromuscular blocking agents should be avoided;
- glucose levels should be target at ≤ 180 mg/dL;
- deep vein thrombosis prevention should be given with low-molecular weight heparin subcutaneously;
- stress ulcer prophylaxis should be applied in patients at risk, using proton pump inhibitors;
- enteral nutrition should be started early (< 48 hours).

In conclusion, sepsis syndrome in urology remains a severe situation with an considerable mortality rate. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next years [172, 193]. Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antimicrobial treatment provide the best conditions for improving patient survival. The prevention of sepsis syndrome is dependent on good practice to avoid nosocomial infections and using antimicrobial prophylaxis and therapy in a prudent and well-accepted manner.

Figure 2: Clinical algorithm for the management of urosepsis



3.10 Urethritis

3.10.1 Introduction

Inflammation of the urethra presents usually with symptoms of the LUT and must be distinguished from other infections of the LUT. The following recommendations are based on a review of several European national guidelines and are aligned with the CDC's guidelines on sexual transmitted diseases (STDs) [194-197].

3.10.2 Epidemiology, aetiology and pathogenesis

From a therapeutic and clinical point of view, *gonorrhoeal urethritis* (GU) must be differentiated from non-*gonococcal urethritis* (NGU). Infection is spread by sexual contact. Causative pathogens include *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG), *Trichomonas vaginalis* (TV), and *Ureaplasma urealyticum* (UU) [198-203]. In a study of 367 patients with NGU isolated causative pathogens were: CT in 22.3%, MG in 12.5%, TV in 2.5%, and UU in 24.0%, with multiple pathogens detected in 9.5% and no aetiology in 29.2% [198]. There is limited evidence to support the role of *Mycoplasma hominis* in urethritis [204, 205].

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae* and *C. trachomatis*) and cause pyogenic infection. Although arising from urethritis, chlamydiae and gonococci can spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women [206-208].

Mucopurulent or purulent discharge, alguria, dysuria and urethral pruritus are symptoms of urethritis. However, many infections of the urethra are asymptomatic.

3.10.3 Diagnostic evaluation

A Gram stain of urethral discharge or a urethral smear that shows more than five leukocytes per high power

field ($\times 1,000$) and eventually, gonococci located intracellularly as Gram-negative diplococci, indicate pyogenic urethritis [209]. Laboratories should use validated nucleic acid amplification tests (NAATs) to detect chlamydia and gonorrhoea, in first void urine samples, as they are better than any of the other tests available for the diagnosis of chlamydial and gonococcal infections [210]. *N. gonorrhoeae* and chlamydia cultures are mainly to evaluate treatment failures and monitor developing resistance to current treatment.

In all patients with urethritis, and when sexual transmission is suspected, the aim should be to identify the pathogenic organisms. *Trichomonas* spp. can usually be identified microscopically [208].

3.10.3.1 Recommendations for the diagnostic evaluation of urethritis

Recommendations	LE	GR
Use a gram stain of urethral discharge or a urethral smear to preliminarily diagnosis pyogenic urethritis.	3	B
Use a validated nucleic acid amplification tests to diagnosis chlamydial and gonococcal infections.	3	B

3.10.4 Disease management

Broad spectrum empirical antibiotic therapy may be started on presentation followed by antibiotic treatment refinement according to the results of microbiological investigations.

3.10.4.1 Recommendations for antimicrobial therapy of Urethritis [211, 212]

Pathogen	Antimicrobial	Dosage & Duration of therapy	LE	GR	Alternative regimens
<i>Gonococcal Infection</i>	Ceftriaxone	1 g i.m., SD	1a	A	Cefixime 400 mg p.o., SD Or Azithromycin 1-1.5 g p.o., SD
	Azithromycin	1-1.5 g p.o., SD			
	Cefixime	800 mg p.o., SD			
<i>Non-Gonococcal infection (non-identified pathogen)</i>	Doxycycline	100 mg b.i.d, p.o., 7-10 days	1b	A	Azithromycin 0.5 g p.o., day 1, 250 mg p.o., days 2-5
<i>Chlamydia trachomatis</i>	Azithromycin	1.0-1.5 g p.o., SD	1b	A	Doxycycline 100 mg b.i.d, p.o., for 7 days
<i>Mycoplasma genitalium</i>	Azithromycin	0.5 g p.o., day 1, 250 mg p.o., day 2-5	2a	B	Moxifloxacin 400 mg q.d., 5 days however, because of reported failures, some experts recommend 10 -14 days
<i>Ureaplasma urealyticum</i>	Doxycycline	100 mg b.i.d, p.o., 7 days	1b	A	Azithromycin 1.0-1.5 g p.o., single dose Or Clarithromycin 500 mg b.i.d, 7 days (resistance against macrolides is possible)
<i>Trichomonas vaginalis</i>	Metronidazole	2 g p.o., SD	1a	A	In case of persistence 4 g daily for 3-5 days

SD = single dose; b.i.d = twice daily; q.d = everyday; p.o. = orally, i.m. = intramuscular.

3.10.5 Follow-up

Patients should be followed-up for control of eradication or if symptoms persist or recur after completion of therapy. Patients should be instructed to abstain from sexual intercourse for seven days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Reporting and source tracing should be done in accordance with national guidelines and in co-operation with specialists in venereology, whenever required. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV.

3.11 Bacterial Prostatitis

3.11.1 Introduction

Bacterial prostatitis is a clinical condition caused by bacterial infection of the prostate gland. It is

recommended that urologists use the classification suggested by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in which bacterial prostatitis, with confirmed or suspected infection, is distinguished from chronic pelvic pain syndrome (CPPS) (Table 4) [213-215].

Table 4: Classification of prostatitis and CPPS according to NIDDK/NIH [213-215]

Type	Name and description
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic abacterial prostatitis – chronic pelvic pain syndrome
IIIA	Inflammatory chronic pelvic pain syndrome (white cells in semen/expressed prostatic secretion/voided bladder urine 3)
IIIB	Non-inflammatory chronic pelvic pain syndrome (no white cells in semen/expressed prostatic secretion/voided bladder urine 3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

3.11.2 **Epidemiology, aetiology and pathogenesis**

A causative pathogen is detected by routine methods in only 5-10% of cases [216], antimicrobial therapy in these patients therefore, has a rational basis [217, 218]. The remainder of patients are treated empirically with numerous medical and physical modalities. However, recent improvement in classification and application of modern methods, including molecular biology, should allow proper systematisation of treatment [218, 219]. Enterobacteriaceae, especially *E. coli*, are the predominant pathogens in acute bacterial prostatitis [220]. In chronic bacterial prostatitis, the spectrum of strains is wider [218]. In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis*, *Candida sp.* and rare pathogens, such as *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum* [221]. The significance of intracellular bacteria, such as *C. trachomatis*, is uncertain [222] however, two studies have highlighted its role as a causative pathogen in chronic bacterial prostatitis [223, 224].

3.11.3 **Diagnostic evaluation**

3.11.3.1 **History and symptoms**

According to the duration of symptoms, bacterial prostatitis is described as either acute or chronic, the latter being defined by symptoms that persist for at least three months [225-227]. The predominant symptoms are pain at various locations (Table 5) and LUTS such as a frequent need to urinate, difficulty urinating e.g. weak stream, straining and pain on urination, or that increases during urination [213-215]. Chronic bacterial prostatitis is the most frequent cause of rUTI in men [228].

Table 5: Localisation of pain in patients with prostatitis like symptoms [215]

Site of pain	Percentage of patients
Prostate/perineum	46%
Scrotum and/or testes	39%
Penis	6%
Urinary bladder	6%
Lower back	2%

3.11.3.2 **Symptom questionnaires**

Symptoms appear to have a strong basis for use as a classification parameter in bacterial prostatitis [229]. Prostatitis symptom questionnaires have therefore been developed for the quantification of symptoms [229, 230]. They include the Chronic Prostatitis Symptom Index (CPSI), which was recently developed by the International Prostatitis Collaborative Network (IPCN), initiated by the NIH [231]. The questionnaire contains four questions regarding pain or discomfort, two regarding urination, and three related to quality of life.

3.11.4 **Clinical findings**

In acute prostatitis, the prostate may be swollen and tender on DRE. Prostatic massage is contraindicated. Otherwise, the prostate is usually normal on palpation. In case of lasting symptoms ("chronic prostatitis" symptoms) CPPS as well as other urogenital and ano-rectal disorders must be taken into consideration. Symptoms of chronic prostatitis or CPPS can mask prostate tuberculosis. Pyospermia and haemospermia in

men in endemic regions or with a history of tuberculosis should prompt investigation for urogenital tuberculosis [218].

3.11.4.1 Urine cultures and expressed prostatic secretion

The most important investigation in the evaluation of a patient with acute prostatitis is MSU culture [232]. If the patient presents with clinical signs suggestive of blood-stream infection, a blood culture should be taken following local protocols. In chronic bacterial prostatitis, quantitative bacteriological localisation cultures and microscopy of the segmented urine and of expressed prostatic secretion (EPS), as described by Meares and Stamey [217] are important investigations.

3.11.4.2 Prostate biopsy

Perineal biopsies cannot be recommended as routine work-up and should be reserved only for research purposes. Transrectal prostate biopsy is not advisable in bacterial prostatitis [232].

3.11.4.3 Other tests

Transrectal ultrasound (TRUS) may reveal intraprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles but is unreliable and cannot be used as a diagnostic tool in prostatitis [233].

3.11.4.4 Additional investigations

3.11.4.4.1 Ejaculate analysis

An analysis of the ejaculate is not recommended for microbiological investigation due to the low sensitivity and specificity compared to the two or three-glass tests [232]. Ejaculate analysis is however frequently involved as part of the investigation of a generalised male accessory gland infection. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

3.11.4.4.2 Prostate specific antigen

Prostate specific antigen (PSA) is often increased in acute bacterial prostatitis and other urogenital infections. If a patient has elevated PSA and evidence of prostatic inflammation, serum PSA will normalise after antimicrobial treatment of four weeks in about 50% of patients [234]. A delay of at least three months should be allowed before it can be assumed that a stable level of PSA has been reached. Measurement of free and total PSA adds no practical diagnostic information in prostatitis [235].

3.11.5 Recommendations for the diagnostic evaluation of bacterial prostatitis

Recommendations	LE	GR
Perform digital rectal examination to assess the condition of the prostate.	4	A*
Take a mid-stream urine culture in patients with acute prostatitis-related symptoms for diagnosis and targeted treatment planning.	3	A*
Perform the Meares and Stamey four-glass test in patients with chronic bacterial prostatitis.	2b	B
Accurate microbiological evaluation for atypical pathogens such as <i>Chlamydia trachomatis</i> or <i>Mycoplasma</i> is recommended in patients with chronic bacterial prostatitis.	2b	B
Perform transrectal ultrasound only in selected cases to rule out the presence of prostatic abscess, calcification in the prostate and dilatation of the seminal vesicles.	3	B
Ejaculate analysis and prostate specific antigen measurement should not be performed as routine, due to the high number of false positive results.	3	B

*Upgraded based on panel consensus.

3.11.6 Disease management

3.11.6.1 Antimicrobials

Antimicrobials are life-saving in acute bacterial prostatitis and recommended in chronic bacterial prostatitis.

Acute bacterial prostatitis is a serious infection with fever and intense localised and general pain. Parenteral administration of high doses of bactericidal antimicrobials, such as a broad-spectrum penicillin, a third-generation cephalosporin or a fluoroquinolone, is recommended [232]. For initial therapy, any of these antimicrobials may be combined with an aminoglycoside [218, 232]. After defervescence and normalisation of infection parameters, oral therapy can be substituted in and continued for a total of two to four weeks [236].

Fluoroquinolones, such as ciprofloxacin and levofloxacin, are considered drugs of choice because of their favourable pharmacokinetic properties [237], their generally good safety profile, and antibacterial activity against Gram-negative pathogens, including *Pseudomonas aeruginosa*. In addition, levofloxacin is

active against Gram-positive and atypical pathogens, such as *C. trachomatis* and genital mycoplasmas.

The duration of antimicrobial treatment is based on clinical experience [238]. In chronic bacterial prostatitis antimicrobials should be given for four to six weeks after initial diagnosis [218, 232]. Relatively high doses are needed and oral therapy is preferred [237, 238]. If intracellular bacteria have been detected or are suspected, tetracyclines or erythromycin should be given [237, 239].

3.11.6.2 Recommendations for the disease management of bacterial prostatitis

Antimicrobial	Daily dose	Duration of therapy	LE	GR	Comments
Acute febrile bacterial prostatitis with symptoms and fever					
Levofloxacin	500 mg q.d	All parental treatment should be given until defervescence	2	B	All of these antimicrobials can be administered in conjunction with aminoglycosides e.g. Gentamicin 5 mg/kg q.d or Amikacin 15 mg/kg q.d.
Ciprofloxacin	500 mg b.i.d				
Ceftriaxone	2 g q.d				
Piperacillin/tazobactam	4.5 g t.i.d				
Cefepime	2 g b.i.d				
Acute afebrile bacterial prostatitis with symptoms or after defervescence					
Levofloxacin	500 mg q.d	2-4 weeks	2	B	
Ciprofloxacin	500 mg b.i.d or 1000 mg p.d	2-4 weeks			
Trimethoprim	200 mg b.i.d	2-4 weeks			
Co-trimoxazole	960 mg b.i.d	2-4 weeks			
Doxycycline	100 mg b.i.d	10 days	2	B	Only for <i>Chlamydia trachomatis</i> or mycoplasma infections.
Chronic bacterial prostatitis					
Levofloxacin	500 mg q.d	4-6 weeks	3	B	
Ciprofloxacin	500 mg b.i.d or 1000 mg q.d	4-6 weeks			
Trimethoprim	200 mg b.i.d	4-6 weeks			
Co-trimoxazole	960 mg b.i.d	4-6 weeks			
Doxycycline	100 mg b.i.d	10 days	2	B	Only for <i>Chlamydia trachomatis</i> or mycoplasma infections.

b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

3.11.6.3 Intraprostatic injection of antimicrobials

This treatment has not been evaluated in controlled trials and should not be considered [240, 241].

3.11.6.4 Drainage and surgery

Approximately 10% of men with acute prostatitis will experience urinary retention [242] which can be managed by suprapubic, intermittent or indwelling catheterisation. Suprapubic cystostomy placement is generally recommended. The use of catheterisation without evidence of retention may increase the risk of progression to chronic prostatitis [243]. Alpha-blocker treatment has also been recommended, but clinical evidence of benefit is poor [218, 232].

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible [244]. The size may matter. In one study conservative treatment was successful if the abscess cavities were < 1 cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage [245].

3.11.7 Follow-up

In asymptomatic post-treatment patients routine urinalysis and/or urine culture is not mandatory. The Meares and Stamey four-glass test should be repeated in patients representing with persistent symptoms. In patients with persistent symptoms and repeated positive microbiological results for sexually transmitted infectious pathogens, microbiological screening of the patients partner(s) is recommended [218, 232].

3.12 Acute Infective Epididymitis

3.12.1 Evidence question

In men with acute epididymitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?

3.12.2 **Epidemiology, Aetiology and Pathophysiology**

Epididymitis is a common condition with incidence ranging from 25 to 65 cases per 10,000 adult males per year and can be acute, chronic or recurrent [246]. Acute epididymitis is clinically characterised by pain, swelling and increased temperature of the epididymis, which may involve the testis and scrotal skin. It is generally caused by migration of pathogens from the urethra or bladder. Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis in boys and young men.

The predominant pathogens isolated are *C. trachomatis*, Enterobacteriaceae (typically *E. coli*) and *N. gonorrhoeae* [247]. Men who have anal intercourse and those with abnormalities of the urinary tract resulting in bacteriuria are at higher risk of epididymitis caused by Enterobacteriaceae. The mumps virus should be considered if there are viral prodromal symptoms and salivary gland enlargement. Tuberculous epididymitis may occur in high-risk groups such as men with immunodeficiency and those from high prevalence countries, it frequently results in a discharging scrotal sinus. *Brucella* or *Candida* species are rare possible pathogens.

3.12.3 **Diagnostic Evaluation**

Culture of a mid-stream specimen of urine should be performed and any previous urine culture results should be checked. Sexually transmitted infection with *C. trachomatis* or *N. gonorrhoeae* should be detected by NAAT on first voided urine. A urethral swab or smear should be performed for Gram staining and culture if *N. gonorrhoeae* is likely. Detection of these pathogens should be reported according to local arrangements. All patients with probable STI should be advised to attend an appropriate clinic to be screened for other sexually transmitted infections. Men with Enterobacteriaceae may require investigation for lower urinary tract abnormalities. If tuberculous epididymitis is suspected, three sequential early morning urine samples should be cultured for acid-fast bacilli (AFB) and sent for screening by NAAT for *M. tuberculosis* DNA [248]. Prostate secretion, ejaculate, discharge from a draining scrotal fistula, as well as fine needle aspiration and biopsy specimens should be investigated using microscopy, AFB culture and NAAT, respectively.

3.12.4 **Disease Management**

Men with suspected STI should be informed of the risks to others and advised not to have sex until free of infection. Empirical antimicrobial therapy has to be chosen by consideration of the most probable pathogen and degree of penetration into the inflamed epididymis and may need to be varied according to local pathogen sensitivities and guidance. Generally, both *C. trachomatis* and Enterobacteriaceae should be covered initially and the regimen modified according to pathogen identification. Doxycycline and some specific fluoroquinolones have good clinical and microbiological cure rates in patients with suspected *C. trachomatis* and both achieve adequate levels in inflamed male genital tissues with oral dosing. Macrolide antibiotics such as azithromycin are effective against *C. trachomatis* but not tested in epididymitis. Fluoroquinolones remain effective for oral treatment of Enterobacteriaceae although resistance is increasing and local advice should be sought. Fluoroquinolones should not be considered for gonorrhoea. Single high parenteral dose of a third generation cephalosporin is effective against *N. gonorrhoeae*; current resistance patterns and local public health recommendations should guide choice of agent.

Clinical response to antibiotics in men with severe epididymitis should be assessed after about three days and men with likely or proven STI should be assessed at fourteen days to check cure and ensure tracing and treatment of contacts according to local public health recommendations.

3.12.5 **Evidence Summary**

Relating to this chapter three guidelines based on systematic reviews were identified [249-251] with search dates of December 2009, March 2012 and April 2013 respectively. A structured search of the literature from January 2010 to March 2015 identified 553 titles of which 45 were selected for full text review and five were included [252-256]. Data from a large comparative case series suggested that young age and history of sexual activity are not sufficiently predictive of a sexually transmitted pathogen to guide antibiotic treatment in acute epididymitis [256].

Empiric antibiotic regimens from existing guidelines [249-251] and panel consensus:

1. For men with acute epididymitis at low risk of gonorrhoea (e.g. no discharge) a single agent or combination of two agents of sufficient dose and duration to eradicate *C. trachomatis* and Enterobacteriaceae should be used. Appropriate options are:
 - A. A fluoroquinolone active against *C. trachomatis* orally once daily for ten to fourteen days*
 - OR**
 - B. Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days* **plus** an antibiotic active against Enterobacteriaceae** for ten to fourteen days*

2. For men with likely gonorrhoeal acute epididymitis a combination regimen active against *Gonococcus* and *Chlamydia trachomatis* must be used such as:
 - A. Ceftriaxone 500 mg intramuscularly single dose **plus**
Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days*
3. For non-sexually active men with acute epididymitis a single agent of sufficient dose and duration to eradicate Enterobacteriaceae should be used. Appropriate option is a fluoroquinolone by mouth once daily for ten to fourteen days*

*Depending upon pathogen identification and clinical response.

** A parenteral option will be required for men with severe infection requiring hospitalisation.

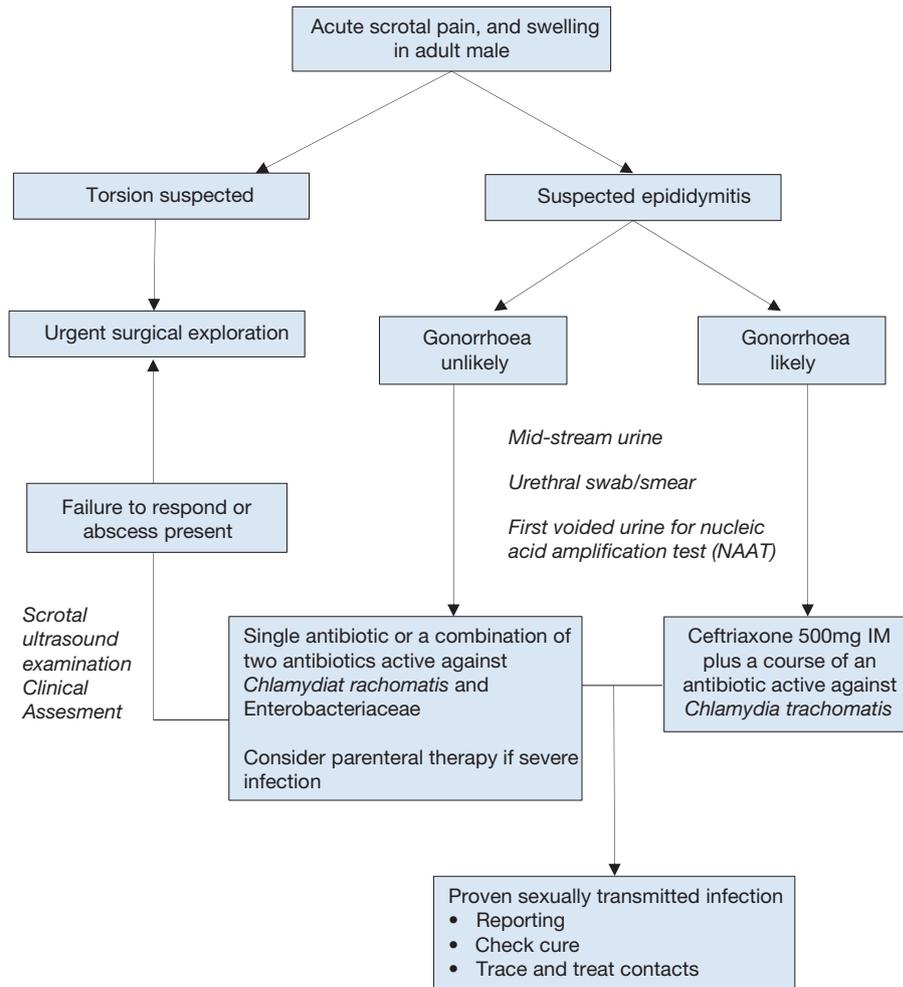
Surgical exploration may be required to drain abscesses or debride tissue. A comparative cohort study found that lack of separation of epididymis and testis on palpation and the presence of abscess on US may predict requirement for surgery following initial antibiotic treatment [252].

A cohort study found semen parameters may be impaired during epididymitis but recovered following successful treatment [255]. Comparative clinician cohort studies suggest adherence to guidelines for assessment and treatment of epididymitis is low, particularly by urologists compared to sexual health specialists [253] and by primary care physicians [254].

3.12.6 Recommendations for the treatment of acute infective epididymitis

Recommendations	LE	GR
Obtain a mid-stream urine and first voided urine for pathogen identification.	3	A*
Initially prescribe a single antibiotic or a combination of two antibiotics active against <i>Chlamydia trachomatis</i> and Enterobacteriaceae in young sexually active men; in older men without sexual risk factors only Enterobacteriaceae have to be considered.	3	A*
If gonorrhoeal infection is likely, give single dose ceftriaxone 500 mg intramuscularly in addition to a course of an antibiotic active against <i>Chlamydia trachomatis</i> .	3	A*
Adjust antibiotic agent when pathogen has been identified and adjust duration according to clinical response.	3	A*
Follow national policies on reporting and tracing/treatment of contacts for sexually transmitted infections.	3	A*

* Upgraded based on Panel consensus.

Figure 3: Diagnostic and treatment algorithm for adult men with acute epididymitis.

3.13 Fournier's Gangrene

3.13.1 Introduction

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia [257]. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway. Evidence regarding investigation and treatment is predominantly from case series.

3.13.2 Diagnostic evaluation

Fournier's gangrene remains rare but its incidence is increasing with an ageing population and higher prevalence of diabetes, and emergence of multi-resistant pathogens. Typically there is painful swelling of the scrotum or perineum with severe sepsis [258]. Examination shows small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease [259]. Risk factors include immuno-compromised patients, most commonly diabetes or malnutrition, or a recent history of catheterisation, instrumentation or perineal surgery. In up to 40% of cases, the onset is more insidious with undiagnosed pain often resulting in delayed treatment [260, 261]. A high index of suspicion and careful examination, particularly of obese patients, is required.

3.13.2.1 Microbiology

Fournier's gangrene is typically a type 1 necrotising fasciitis that is polymicrobial in origin, including *S.aureus*, *Streptococcus* sp., *Klebsiella* sp., *E. coli* and anaerobes; involvement of *Clostridium* sp. is now less common [258, 260, 262]. These organisms secrete endotoxins causing tissue necrosis and severe cardiovascular impairment. Subsequent inflammatory reaction by the host contributes to multi-organ failure and death if untreated.

3.13.3 Disease management

The degree of internal necrosis is usually vastly greater than suggested by external signs, and consequently,

adequate, repeated surgical debridement is necessary to save the patient's life [263]. Disease-specific severity scoring systems do not appear superior to generic critical illness scores and are therefore not recommended for routine use [264-266]. Computed tomography or MRI can help define para-rectal involvement, suggesting the need for colostomy [267]. Consensus from case series suggests that surgical debridement should be early (< 24 hours) and complete, as delayed and/or inadequate surgery results in higher mortality [268]. Concurrent parenteral antibiotic treatment should be given that covers all causative organisms and can penetrate inflammatory tissue. This can then be refined following surgical cultures. The benefit of pooled immunoglobulin therapy and hyperbaric oxygen remains uncertain and should not be used routinely [267, 269, 270]. With aggressive early surgical and medical management, survival rates are > 70% depending upon patient group and availability of critical care [271]. Following resolution, reconstruction using skin grafts is required [272-275].

3.13.3.1 Recommendations for the disease management of Fournier's Gangrene

Recommendations	LE	GR
Commence full, repeated, surgical debridement within 24 hours of presentation.	3	B
Start treatment with broad-spectrum antibiotics on presentation, with subsequent refinement according to culture and clinical response.	3	A*
Do not use adjunctive treatments such as pooled immunoglobulin and hyperbaric oxygen, except in the context of clinical trials.	3	A*

* Upgraded based on panel consensus.

3.14 Detection of bacteriuria prior to urological procedures

3.14.1 Evidence question

What is the diagnostic accuracy of alternative urinary investigations compared with urine culture for the diagnosis of bacteriuria in adult patients prior to urological interventions?

3.14.2 Background

Identifying bacteriuria prior to diagnostic and therapeutic procedures aims to reduce the risk of infectious complications by controlling any pre-operative detected bacteriuria and to optimise antimicrobial coverage in conjunction with the procedure. However, the absence of bacteriuria by itself is not an assurance against infectious complications and antimicrobial prophylaxis according to section 3.15 is recommended.

The standard method, laboratory culture of an appropriate urine sample, is time consuming and logistically difficult. Alternative rapid near-patient methods such as reagent strip (dipstick) urinalysis, automated microscopy, flow cytometry, and dipslide culture have been developed but their diagnostic accuracy is uncertain.

3.14.3 Evidence summary

A systematic search of the literature to February 2015 identified 3,033 titles of which 210 were selected for full text review and 18 studies investigating diagnostic accuracy of different index tests with urine culture as the reference standard were included [276-293]. None of the studies focused on a urology patient population.

3.14.3.1 Reagents strip (dipstick) urinalysis

Sixteen studies assessed dipstick urine analysis using a variety of criteria for a positive test [276-284, 287-289]. The criterion that resulted in the best overall diagnostic accuracy was when a positive test was defined as at least one of nitrite and leucocyte esterase being detected however, low sensitivity (0.8) limits clinical usefulness, in the setting of assessment of bacteriuria, prior to urological surgery.

3.14.3.2 Automated microscopy

Two studies used automated microscopy of urine sediment following centrifugation [285, 289]. Although sensitivity was high (0.98), specificity was too low for effective use in this setting (0.59) and optimum diagnostic thresholds were not determined.

3.14.3.3 Dipslide culture

Two studies on dipslide technology using different culture media were identified [286, 293]. In one study diagnostic accuracy was high (0.98) although contaminated samples were excluded [31]. The other study showed lower accuracy, below the level required in this setting [286]. Overall, dipslide technology is currently unsuited for routine use in this setting with further studies required to determine the best combination of culture media.

3.14.3.4 Flow cytometry

No studies on this technology that met the inclusion criteria. The poor quality of available studies was confirmed in a meta-analysis [294]. In summary, laboratory urine culture remains the standard investigation to detect both the presence and absence of clinically relevant concentrations of bacteria in urine.

Recommendation	LE	GR
Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients prior to undergoing urological interventions.	3	B

3.15 Peri-operative antibacterial prophylaxis in urology

3.15.1 Introduction

The aim of antimicrobial prophylaxis (AMP) in urology is to prevent infectious complications resulting from diagnostic and therapeutic procedures. However, evidence for the best choice of antimicrobials and regimens is limited.

As microbial resistance is dramatically increasing, there is a strong need to change unproven paradigms. In the absence of high level evidence regarding the benefit of AMP, prior to a specific procedure, the Guideline panel recommends to individually assess its need for each case. It is important to keep in mind that AMP is only one of several measures to prevent infections and can never compensate for poor hygiene and operative technique. The CDC has presented definitions that are currently the most comprehensive, and are recommended for the evaluation of infectious complications [295]. These definitions have also been used in the Global Prevalence Study on Infections in Urology (GPIU) point prevalence studies [296].

3.15.2 Risk factors

The risk of infection varies with the type of intervention. The wide spectrum of interventions and the recent advances in minimal invasive surgery have further complicated the provision of clear-cut recommendations. Furthermore, the bacterial load, the duration and difficulty of the procedure, the surgeon's skill, and peri-operative bleeding may also influence the risk of infection [295, 297, 298]. For elective urological surgery, general and urinary-tract-specific risk factors must be controlled (i.e. bacteriuria, obstruction).

Before surgery, it is essential to categorise the patients in relation to:

- their general health status according to the American Society of Anaesthesiology (ASA) score P1-P5;
- the presence of general risk factors such as older age, diabetes mellitus, impaired immune system, malnutrition, extreme weight; even though these risk factors were not proven in level one evidence studies;
- the presence of specific endogenous or exogenous risk factors such as a history of UTI or urogenital infection, indwelling catheters, bacterial burden, previous instrumentation, genetic factors;
- the type of intervention and surgical field contamination burden;
- the expected level of invasiveness, duration and technical aspects of the procedure.

3.15.3 Principles of antimicrobial prophylaxis

3.15.3.1 Timing

Overall, administration of the first dose of antimicrobial within 60 minutes before surgical incision is recommended. Administration of vancomycin and fluoroquinolones should begin within 120 minutes before surgical incision due to the prolonged infusion times required for these drugs [299, 300].

3.15.3.2 Route of administration

The preferred route of administration varies with the type of procedure, however, for a majority of procedures, intravenous administration is ideal as it produces rapid, reliable, and predictable serum and tissue concentrations [299, 300].

3.15.3.3 Duration of the regimen

For most procedures, duration of AMP has not yet been adequately addressed and rarely can a defined regimen be recommended. In principle, the duration of peri-operative prophylaxis should be minimised, ideally to a single dose.

3.15.3.4 Choice of antimicrobials

No clear-cut recommendations can be given, as there is considerable variation in Europe regarding bacterial spectra and their susceptibility to different antimicrobials. Therefore, knowledge of the local pathogen profiles, susceptibility and virulence is mandatory in establishing local AMP guidelines. It is also essential to define the

predominant pathogens for each type of procedure. When choosing an antimicrobial agent, it is necessary to consider the procedure-specific risk factors, contamination load, target organ, and the role of local inflammation.

3.15.4 **Antimicrobial prophylaxis by procedure**

3.15.4.1 *Diagnostic procedures*

3.15.4.1.1 Transrectal prostate biopsy

See section 3.16 for the results of a recent systematic review on which strategies are effective for reducing the risk of infective complications in men undergoing prostate biopsy.

3.15.4.1.2 Cystoscopy

The frequency of infectious complications after cystoscopy, standard urodynamic studies and diagnostic simple ureteroscopy in otherwise healthy individuals with sterile pre-operative urine is low [301-303]. In view of the very large number of cystoscopic examinations, the low infectious risk and the potential adverse effect on bacterial sensitivity, AMP is not recommended. However, bacteriuria, indwelling catheters, neurogenic LUTD and a history of urogenital infection are risk factors that must be considered [304-317].

3.15.4.2 *Endourological treatment procedures (urinary tract entered)*

3.15.4.2.1 Transurethral resection of the bladder (TURB)

There is little evidence for any benefit of AMP prior to TURB. Studies do not distinguish between simple fulguration (cystoscopy) and large or multiple tumours, or the presence or absence of necrotic material. Therefore, the present Guidelines recommend that clinicians choose the appropriate AMP regime based on tumour differentiation, see section 3.15.5 [303, 318-320].

3.15.4.2.2 Transurethral resection of the prostate (TURP)

Transurethral resection of the prostate is the best studied urological intervention. At least two meta-analyses of a large number of prospective, randomised controlled studies, including several thousand patients, showed a marked benefit of AMP with a relative risk reduction of 65% and 77% for bacteriuria and septicaemia, respectively [303, 318-320].

3.15.4.2.3 Ureteroscopy

Well-conducted prospective controlled trials on ureteroscopy are lacking. It is reasonable, however, to distinguish low-risk procedures, such as simple diagnostic and distal stone treatment in otherwise healthy individuals, from higher-risk procedures, such as treatment of proximal impacted stones with obstruction. Therefore the present Guidelines recommend clinicians choose the appropriate AMP regime based on the degree of severity, stone anatomic position and patient related risk factors, all of which are supported by a large database study [321].

3.15.4.2.4 Percutaneous nephrolithotripsy (PNL)

The risk of infection in PNL is high and use of AMP has been shown to significantly reduce the risk of infectious complications [99, 322-329]. A single dose was shown to be sufficient [330]. Retrograde intra-renal stone treatment could be expected to have a similar risk profile [321].

3.15.4.2.5 Shock-wave lithotripsy

No standard AMP is recommended. However, control of bacteriuria and AMP is recommended in cases of increased bacterial burden (e.g. indwelling catheter, nephrostomy tube, or infectious stones) [331-340].

3.15.4.3 *Laparoscopic surgery*

There has been a lack of sufficiently powered studies in laparoscopic urological surgery. However, it seems reasonable to manage laparoscopic surgical procedures in the same manner as the corresponding open procedures.

3.15.4.4 *Nephrectomy, adrenalectomy*

No standard AMP can be recommended, however, AMP may be considered optional in certain circumstances [341-345].

3.15.4.5 *Prostatectomy*

In open enucleation of prostatic adenoma, the risk of post-operative infection is particularly high and AMP is recommended [346]. As there are no studies on AMP in radical prostatectomy the use of AMP may be considered optional.

3.15.4.6 Cystectomy with bowel use

Single or one day dosage AMP is recommended, although prolonged operation and other morbidity risk factors might support the use of pre-emptive antimicrobial treatment, which should be < 72 hours. The choice of antimicrobials should focus on aerobic and anaerobic pathogens. Evidence is based on colorectal surgery, but experience is limited for specific urological interventions [347-350].

3.15.4.7 Post-operative drainage of the urinary tract

When continuous urinary drainage is left in place after surgery, prolongation of AMP is not recommended. Asymptomatic bacteriuria should not be treated.

3.15.4.8 Implantation of prosthetic devices: testis, penile prosthesis and artificial sphincter

Antimicrobial prophylaxis is recommended. When infectious complications occur in implant surgery, they are usually problematic and often result in removal of the prosthetic device. Diabetes mellitus is considered a specific risk factor for infection. Skin-related staphylococci are responsible for most infections, AMP used must be chosen to target these strains [351-354].

3.15.5 Recommendations for peri-operative antibacterial prophylaxis in urology

Recommendations				
Procedure	Comments	Antimicrobial prophylaxis	LE	GR
Diagnostic procedures				
Cystoscopy	Low frequency of infection. Consider individual risk factors for UTI (i.e. asymptomatic bacteriuria, history of febrile UTI)	No	1b	A
Urodynamic study	Low frequency of infections. Consider individual risk factors for UTI (i.e. asymptomatic bacteriuria, history of febrile UTI)	No	1a	A
Transrectal core biopsy of prostate	High risk of infection	Fluoroquinolones Trimethoprim ± sulphamethoxazole Targeted alternative	1b	A
Diagnostic ureteroscopy	No available studies	Optional	4	C
Common endourological/endoscopic therapeutic procedures (examples)				
Fulguration of small bladder tumours	Low frequency of infections.	Optional	2b	C
Transurethral resection of the bladder	Poor data. No concern given to burden of tumour, i.e. size, multiplicity, necrosis	Trimethoprim ± sulphamethoxazole Aminopenicillin/ Beta-lactamase inhibitor Cephalosporin group 2 or 3	2b	C
Transurethral resection of the prostate	High risk of infection		1a	A
Shock-wave lithotripsy	Low frequency of infections		1a	A
Ureteroscopy for stone management	Distal stone removal.		2b	B
Percutaneous and retrograde intra-renal stone management	High risk of infection		1b	A
Common open and/or laparoscopic surgery				
Nephrectomy ± ureterectomy Adrenalectomy Radical prostatectomy	Surgical site infection/wound infection poorly documented Secondary post-operative catheter-related asymptomatic bacteriuria/ UTI	Optional	3	C
Planned scrotal surgery, vasectomy, surgery for varicocele	Conflicting data	No	3	C

Prosthetic implants, artificial sphincter	Limited documentation	Aminopenicillin/ Beta-lactamase inhibitor Piperacillin/Tazobactam	3	B
Uretero-pelvic junction repair		Optional	4	C
Partial bladder resection		Optional	3	C
Cystectomy with urine deviation	High risk of infection	Cefuroxim Aminopenicillin/ Beta-lactamase inhibitor + Metronidazole	2a	B

3.16 Prostate biopsy

3.16.1 Evidence question

Which strategies are effective for reducing the risk of infective complications in men undergoing prostate biopsy?

3.16.2 Epidemiology, Aetiology and Pathophysiology

Histological examination of needle biopsies of the prostate is the principle method for prostate cancer diagnosis. Prostate biopsy is a common procedure in high-resource countries with, for example, about 32,000 procedures performed in England during 2013 [355] giving a rate of 2.6/1,000 men at risk per year. Transrectal ultrasound-guided biopsy (TRUS) is the current standard technique although the transperineal route is also used [356]. Infection is the most clinically significant harm experienced by men following prostate biopsy. There is some evidence that the risk is increasing [357]. Infection generally occurs by implantation of rectal commensal organisms into the prostate, urethra or bloodstream during needle insertion. Severity of infection will depend on bacterial inoculum, virulence and status of host defence.

3.16.3 Diagnostic Evaluation

Urine culture prior to prostate biopsy has an uncertain predictive value [358].

3.16.4 Disease Management

The focus is on prevention of infectious complications. Possible strategies include antimicrobial prophylaxis and non-antimicrobial strategies, the effectiveness of which will be described in this section. Established infection is treated according to standard pathways [355].

3.16.5 Evidence summary

A systematic search of the literature to March 2015 identified 1,556 titles of which 189 were selected for full text review and 93 RCTs were included [359-453]

3.16.6 Non-antimicrobial interventions

3.16.6.1 Number of biopsy cores

Meta-analysis of seven trials involving 1,290 men found no evidence that extended biopsy (> 6-24 cores) templates resulted in more infectious complications than standard templates (6-12 cores) [RR (95% CIs) = 1.71 (0.70 – 4.16)] [359-365].

3.16.6.2 Peri-prostatic injection of local anaesthetic

A meta-analysis of 25 RCTs with 3,533 participants found no evidence that use of peri-prostatic injection of local anaesthesia resulted in a higher rate of infectious complications compared to no injection [366-370, 372-388, 429, 430, 434]. Four other RCTs with 497 patients compared different numbers of injections performed for peri-prostatic injection of local anaesthetic. Here, no difference was found in infective complications [RR (95% CIs) = 1.51 (0.26 – 8.97)] [405-408]

3.16.6.3 Route of biopsy

Three RCTs involving 646 men compared transrectal and transperineal routes of biopsy. Overall two men (0.4%) suffered infectious complications after transperineal biopsy, compared to five (1.1%) after transrectal biopsy [RR (95% CIs) = 0.45 (0.10 – 1.97)]. The studies were heterogeneous in design, did not state how infectious outcomes were assessed and used differing antimicrobial prophylaxis between arms.

3.16.6.4 Rectal preparation

A meta-analysis of three studies including 209 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications [RR (95% CIs) = 0.76

(0.40 to 1.46)] [400, 447, 450].

Meta-analysis of six trials including 1,373 men showed that use of a rectal povidone-iodine preparation before biopsy in addition to antimicrobial prophylaxis resulted in a lower rate of infectious complications [RR (95% CIs) = 0.58 (0.43 to 0.76)] [392-397]. Single RCTs showed no evidence of benefit for perineal skin disinfection [398] but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [453].

3.16.6.5 Other interventions

Combining data from two RCTs with 253 participants showed that biopsy using disposable needle guides resulted in nine infectious complications compared to 22 with reusable biopsy needle guides. The difference was not significant [RR (95% CIs) = 0.51 (0.24 to 1.06)] [402, 403]. A single RCT found no evidence that disinfection of a single patient use needle between cores resulted in fewer infectious complications [404]. Another single study evaluated the needle size and did not find significant differences between a 16 G and an 18 G needle size [446].

Recommendation	LE	GR
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	1a	B*

*Downgraded as highest quality trial in meta-analysis showed no difference [391].

3.16.7 Antimicrobial prophylaxis

The meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after biopsy when using AMP as compared to placebo/control [RR (95% CIs) = 0.56 (0.40 to 0.77)] [393, 397, 413, 423, 431, 433, 437, 442, 447, 448, 452]. Thus, antimicrobial prophylaxis is strongly recommended. However, the choice of regimens and duration of prophylaxis remains debatable. Most commonly fluoroquinolones are applied [419, 421, 422, 431, 435, 451]. Due to the increase in fluoroquinolone resistance recent studies have investigated alternatives like fosfomycin trometamol [435], or suggest targeted antimicrobial prophylaxis based on rectal swab [401]. While the available Cochrane review of 2011 suggests a one-day prophylaxis with a single agent [454], a recent systematic analysis has pointed towards an augmented antimicrobial therapy [455]. A meta-analysis on this issue by the guideline panel is ongoing on and will be finalised next year.

Recommendation	LE	GR
Use antimicrobial prophylaxis in men prior to transrectal prostate biopsy.	1a	A

4. REFERENCES

1. Stein, R., *et al.* Urinary tract infections in children: EAU/ESPU guidelines. *Eur Urol*, 2015. 67: 546.
<https://www.ncbi.nlm.nih.gov/pubmed/25477258>
2. Blok, B., *et al.* EAU Guidelines on Neuro-urology. In: EAU Guidelines, edition presented at the annual EAU Congress London 2017. ISBN 978-90-79754-91-5.
3. Koves, B., *et al.* Systematic review on the management of asymptomatic bacteriuria. PROSPERO, 2015. CRD42015016457.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016457
4. MacLennan, S., *et al.* Which strategies are effective for reducing the risk of infective complications in men undergoing prostate biopsy? PROSPERO, 2015. CRD42015026354.
http://www.crd.york.ac.uk/prospéro/display_record.asp?ID=CRD42015026354
5. Phillips B, *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
6. Horan, T.C., *et al.* CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*, 2008. 36: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/18538699>
7. Rubin, R.H., *et al.* Evaluation of new anti-infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of America and the Food and Drug Administration. *Clin Infect Dis*, 1992. 15 Suppl 1: S216.
<https://www.ncbi.nlm.nih.gov/pubmed/1477233>
8. Rubin, U.H.S.E., *et al.* General guidelines for the evaluation of new anti-infective drugs for the treatment of urinary tract infection. The European Society of Clinical Microbiology and Infectious diseases. Taukirchen, Germany, 1993: 240.
9. U.S. Department of Health and Human Services, F.D.A., Center for Drug Evaluation and Research (CDER). Guidance for Industry Uncomplicated Urinary Tract Infections — Developing Antimicrobial Drugs for Treatment, 1998.
<http://www.fda.gov/ohrms/dockets/98fr/2567dft.pdf>
10. U.S. Department of Health and Human Services, F.D.A., Center for Drug Evaluation and Research (CDER). Complicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry, 2015.
<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070981.pdf>
11. Johansen, T.E., *et al.* Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification system. *Int J Antimicrob Agents*, 2011. 38 Suppl: 64.
<https://www.ncbi.nlm.nih.gov/pubmed/22018988>
12. Allerberger, F., *et al.* Antibiotic stewardship implementation in the EU: the way forward. *Expert Rev Anti Infect Ther*, 2009. 7: 1175.
<https://www.ncbi.nlm.nih.gov/pubmed/19968511>
13. Lesprit, P., *et al.* Hospital antibiotic stewardship. *Curr Opin Infect Dis*, 2008. 21: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/18594284>
14. Cefai, C., *et al.* NICE Guideline: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. 2015.
<https://www.nice.org.uk/guidance/ng15>
15. Dohnhammar, U., *et al.* SWEDERS 2010, A report on Swedish antibiotic utilisation and resistance in human medicine. ISBN 978-91-86723-09-5, 2010.
16. Nilholm, H., *et al.* An Audit-Based, Infectious Disease Specialist-Guided Antimicrobial Stewardship Program Profoundly Reduced Antibiotic Use Without Negatively Affecting Patient Outcomes. *Open Forum Infect Dis*, 2015. 2: ofv042.
<https://www.ncbi.nlm.nih.gov/pubmed/26380341>
17. Davey, P., *et al.* Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*, 2013. 4: CD003543.
<https://www.ncbi.nlm.nih.gov/pubmed/23633313>
18. Cai, T., *et al.* Adherence to European Association of Urology Guidelines on Prophylactic Antibiotics: An Important Step in Antimicrobial Stewardship. *Eur Urol*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26001610>
19. Lutay, N., *et al.* Bacterial control of host gene expression through RNA polymerase II. *J Clin Invest*, 2013. 123: 2366.
<https://www.ncbi.nlm.nih.gov/pubmed/23728172>

20. Hansson, S., *et al.* Untreated asymptomatic bacteriuria in girls: II--Effect of phenoxymethylpenicillin and erythromycin given for intercurrent infections. *BMJ*, 1989. 298: 856.
<https://www.ncbi.nlm.nih.gov/pubmed/2497823>
21. Cai, T., *et al.* The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: To treat or not to treat? *Clin Infect Dis*, 2012. 55: 771.
<https://www.ncbi.nlm.nih.gov/pubmed/22677710>
22. Nicolle, L.E., *et al.* Infectious diseases society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis*, 2005. 40: 643.
<https://www.ncbi.nlm.nih.gov/pubmed/15714408>
23. Kass, E.H. Asymptomatic infections of the urinary tract. *Trans Assoc Am Physicians*, 1956. 69: 56.
<https://www.ncbi.nlm.nih.gov/pubmed/13380946>
24. Gleckman, R., *et al.* Reliability of a single urine culture in establishing diagnosis of asymptomatic bacteriuria in adult males. *J Clin Microbiol*, 1979. 9: 596.
<https://www.ncbi.nlm.nih.gov/pubmed/383746>
25. Warren, J.W., *et al.* A prospective microbiologic study of bacteriuria in patients with chronic indwelling urethral catheters. *J Infect Dis*, 1982. 146: 719.
<https://www.ncbi.nlm.nih.gov/pubmed/6815281>
26. Kunin CM. Urinary tract infections: detection, prevention and management. 5th ed. Baltimore: Williams and Wilkins., 1997.
27. Kass, E.H. Pyelonephritis and bacteriuria. A major problem in preventive medicine. *Ann Intern Med*, 1962. 56: 46.
<https://www.ncbi.nlm.nih.gov/pubmed/14454174>
28. Thomsin, H., *et al.* Single dose fosfomycin trometamol versus multiple dose nitrofurantoin in pregnant women with bacteriuria: preliminary results. *Infection*, 1990. 18 Suppl 2: S94.
<https://www.ncbi.nlm.nih.gov/pubmed/2286469>
29. Williams, G.L., *et al.* Urinary concentrating ability in women with asymptomatic bacteriuria in pregnancy. *Br Med J*, 1969. 3: 212.
<https://www.ncbi.nlm.nih.gov/pubmed/5792611>
30. Akarsu, S., *et al.* The clinical efficacy of fosfomycin trometamol versus amoxicillin- clavulanic acid in the treatment of symptomatic and asymptomatic bacteriuria in 3rd trimester pregnancy. *Turk Jinekoloji ve Obstetrik Dernegi Dergisi*, 2010. 7: 107.
<https://www.researchgate.net/publication/282280547>
31. Anderton, K.J., *et al.* High dose, short course amoxycillin in the treatment of bacteriuria in pregnancy. *Br J Clin Pract*, 1983. 37: 212.
<https://www.ncbi.nlm.nih.gov/pubmed/6882650>
32. Campbell-Brown, M., *et al.* Is screening for bacteriuria in pregnancy worth while? *Br Med J (Clin Res Ed)*, 1987. 294: 1579.
<https://www.ncbi.nlm.nih.gov/pubmed/3113538>
33. Kazemier, B.M., *et al.* Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. *Lancet Infect Dis*, 2015. 15: 1324.
<https://www.ncbi.nlm.nih.gov/pubmed/26255208>
34. Bailey, R.R., *et al.* Comparison of single dose with a 5-day course of co-trimoxazole for asymptomatic (covert) bacteriuria of pregnancy. *Aust N Z J Obstet Gynaecol*, 1983. 23: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/6606421>
35. Bayrak, O., *et al.* Is single-dose fosfomycin trometamol a good alternative for asymptomatic bacteriuria in the second trimester of pregnancy? *Int Urogynecol J Pelvic Floor Dysfunct*, 2007. 18: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/16941068>
36. Bint, A., *et al.* A comparative trial of pivmecillinam and ampicillin in bacteriuria of pregnancy. *Infection*, 1979. 7: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/232697>
37. Christopher, L.J., *et al.* A trial of hippuramine in the treatment of bacteriuria of pregnancy. *Ir J Med Sci*, 1969. 8: 331.
<https://www.ncbi.nlm.nih.gov/pubmed/5806178>
38. Elder, H.A., *et al.* The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and the outcome of pregnancy. *Am J Obstet Gynecol*, 1971. 111: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/4937729>

39. Elder, H.A., *et al.* Use of sulfasymazine in the treatment of bacteriuria of pregnancy. *Antimicrob Agents Chemother* (Bethesda), 1966. 6: 142.
<https://www.ncbi.nlm.nih.gov/pubmed/4862162>
40. Estebanez, A., *et al.* Fosfomycin in a single dose versus a 7-day course of amoxicillin- clavulanate for the treatment of asymptomatic bacteriuria during pregnancy. *Eur J Clin Microbiol Infect Dis*, 2009. 28: 1457.
<https://www.ncbi.nlm.nih.gov/pubmed/19768649>
41. Gerstner, G.J., *et al.* Amoxicillin in the treatment of asymptomatic bacteriuria in pregnancy: a single dose of 3 g amoxicillin versus a 4-day course of 3 doses 750 mg amoxicillin. *Gynecol Obstet Invest*, 1989. 27: 84.
<https://www.ncbi.nlm.nih.gov/pubmed/2659442>
42. Gold, E.M., *et al.* Asymptomatic bacteriuria during pregnancy. *Obstet Gynecol*, 1966. 27: 206.
<https://www.ncbi.nlm.nih.gov/pubmed/5325600>
43. Harris, R.E., *et al.* Single-dose antimicrobial therapy for asymptomatic bacteriuria during pregnancy. *Obstet Gynecol*, 1982. 59: 546.
<https://www.ncbi.nlm.nih.gov/pubmed/7070725>
44. Kincaid-Smith, P., *et al.* Bacteriuria in Pregnancy. *Lancet*, 1965. 1: 395.
<https://www.ncbi.nlm.nih.gov/pubmed/14238090>
45. Little, P.J. The incidence of urinary infection in 5000 pregnant women. *Lancet*, 1966. 2: 925.
<https://www.ncbi.nlm.nih.gov/pubmed/4162367>
46. Lumbiganon, P., *et al.* One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: A randomized controlled trial. *Obst Gynecol*, 2009. 113: 339.
<https://www.ncbi.nlm.nih.gov/pubmed/19155904>
47. Masterton, R.G., *et al.* Single-dose amoxycillin in the treatment of bacteriuria in pregnancy and the puerperium--a controlled clinical trial. *Br J Obstet Gynaecol*, 1985. 92: 498.
<https://www.ncbi.nlm.nih.gov/pubmed/3888250>
48. Mulla, N. Bacteriuria in pregnancy. *Obstet Gynecol*, 1960. 16: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/14425118>
49. Olsen, L., *et al.* Single-dose versus six-day therapy with sulfamethizole for asymptomatic bacteriuria during pregnancy. A prospective randomised study. *Dan Med Bull*, 1989. 36: 486.
<https://www.ncbi.nlm.nih.gov/pubmed/2680315>
50. Pathak, U.N., *et al.* Bacteriuria of pregnancy: results of treatment. *J Infect Dis*, 1969. 120: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/5816817>
51. Pedler, S.J., *et al.* Comparative study of amoxicillin-clavulanic acid and cephalixin in the treatment of bacteriuria during pregnancy. *Antimicrob Agents Chemother*, 1985. 27: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/4004191>
52. Pregazzi, R., *et al.* [Single-dose antibiotic therapy of asymptomatic bacteriuria in pregnancy. Results and complications]. *Minerva Ginecol*, 1987. 39: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/3601207>
53. Reeves, D.S. Laboratory and clinical studies with sulfametopyrazine as a treatment for bacteriuria in pregnancy. *J Antimicrob Chemother*, 1975. 1: 171.
<https://www.ncbi.nlm.nih.gov/pubmed/1100589>
54. Robertson, J.G., *et al.* The management and complications of asymptomatic bacteriuria in pregnancy. Report of a study on 8,275 patients. *J Obstet Gynaecol Br Commonw*, 1968. 75: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/5635245>
55. Thomsen, A.C., *et al.* Antibiotic elimination of group-B streptococci in urine in prevention of preterm labour. *Lancet*, 1987. 1: 591.
<https://www.ncbi.nlm.nih.gov/pubmed/2881132>
56. Whalley, P.J., *et al.* Short-term versus continuous antimicrobial therapy for asymptomatic bacteriuria in pregnancy. *Obstet Gynecol*, 1977. 49: 262.
<https://www.ncbi.nlm.nih.gov/pubmed/320525>
57. Wren, B.G. Subclinical renal infection and prematurity. *Med J Aust*, 1969. 2: 596.
<https://www.ncbi.nlm.nih.gov/pubmed/5388374>
58. Forland, M., *et al.* The treatment of urinary tract infections in women with diabetes mellitus. *Diabetes Care*, 1985. 8: 499.
<https://www.ncbi.nlm.nih.gov/pubmed/4053937>
59. Harding, G.K.M., *et al.* Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engl J Med*, 2002. 347: 1576.
<https://www.ncbi.nlm.nih.gov/pubmed/12432044>

60. Kasyan, G., *et al.* Asymptomatic bacteriuria in postmenopausal women with diabetes mellitus. *Cent European J Urol*, 2013. 66: 320.
<https://www.ncbi.nlm.nih.gov/pubmed/24707373>
61. Asscher, A.W., *et al.* The clinical significance of asymptomatic bacteriuria in the nonpregnant woman. *J Infect Dis*, 1969. 120: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/5803281>
62. Giamarellou, H., *et al.* Survival of elderly bacteriuric subjects following long-term quinolone therapy. *J Chemother*, 2007. 19: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/17434828>
63. Nicolle, L.E., *et al.* Bacteriuria in elderly institutionalized men. *N Engl J Med*, 1983. 309: 1420.
<https://www.ncbi.nlm.nih.gov/pubmed/6633618>
64. Nicolle, L.E., *et al.* Outcome following antimicrobial therapy for asymptomatic bacteriuria in elderly women resident in an institution. *Age Ageing*, 1988. 17: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/3260445>
65. Abrutyn, E., *et al.* Does treatment of asymptomatic bacteriuria in older ambulatory women reduce subsequent symptoms of urinary tract infection? *J Am Geriatr Soc*, 1996. 44: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/8600199>
66. Abrutyn, E., *et al.* Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? *Ann Intern Med*, 1994. 120: 827.
<https://www.ncbi.nlm.nih.gov/pubmed/7818631>
67. Boscia, J.A., *et al.* Therapy vs no therapy for bacteriuria in elderly ambulatory nonhospitalized women. *JAMA*, 1987. 257: 1067.
<https://www.ncbi.nlm.nih.gov/pubmed/3806896>
68. Dontas, A.S., *et al.* Short vs. long cotrimoxazole courses in eradicating bacteriuria in the elderly. *J Chemother*, 1992. 4: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/1629748>
69. Giamarellou, H., *et al.* Kinetics and comparative efficacy of ofloxacin versus co-trimoxazole in the asymptomatic bacteriuria of elderly subjects. *Chemotherapy*, 1991. 37 Suppl 1: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/2049961>
70. Nicolle, L.E., *et al.* Prospective randomized comparison of therapy and no therapy for asymptomatic bacteriuria in institutionalized elderly women. *Am J Med*, 1987. 83: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/3300325>
71. Ouslander, J.G., *et al.* Does eradicating bacteriuria affect the severity of chronic urinary incontinence in nursing home residents? *Ann Intern Med*, 1995. 122: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/7717597>
72. Potts, L., *et al.* A double-blind comparative study of norfloxacin versus placebo in hospitalised elderly patients with asymptomatic bacteriuria. *Arch Gerontol Geriatr*, 1996. 23: 153.
<https://www.ncbi.nlm.nih.gov/pubmed/15374159>
73. Renneberg, J., *et al.* Single-day treatment with trimethoprim for asymptomatic bacteriuria in the elderly patient. *J Urol*, 1984. 132: 934.
<https://www.ncbi.nlm.nih.gov/pubmed/6387184>
74. Amari, E.B.E., *et al.* Outcome of treated and untreated asymptomatic bacteriuria in renal transplant recipients. *Nephrology Dialysis Transplantation*, 2011. 26: 4109.
<https://www.ncbi.nlm.nih.gov/pubmed/21592976>
75. Green, H., *et al.* Consequences of treated versus untreated asymptomatic bacteriuria in the first year following kidney transplantation: Retrospective observational study. *Eur J Clin Microbiol Infect Dis*, 2013. 32: 127.
<https://www.ncbi.nlm.nih.gov/pubmed/22918514>
76. Moradi, M., *et al.* Effect of antibiotic therapy on asymptomatic bacteriuria in kidney transplant recipients. *Urol J*, 2005. 2: 32.
<https://www.ncbi.nlm.nih.gov/pubmed/17629893>
77. Kutlu, S.S., *et al.* Is short course of antimicrobial therapy for asymptomatic bacteriuria before urologic surgical procedures sufficient? *J Infect Dev Ctries*, 2012. 6: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/22337843>
78. Grabe, M., *et al.* Controlled trial of a short and a prolonged course with ciprofloxacin in patients undergoing transurethral prostatic surgery. *Eur J Clin Microbiol*, 1987. 6: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/3569248>

79. Olsen, J.H., *et al.* Cefotaxime for prevention of infectious complications in bacteriuric men undergoing transurethral prostatic resection. A controlled comparison with methenamine. *Scand J Urol Nephrol*, 1983. 17: 299.
<https://www.ncbi.nlm.nih.gov/pubmed/6196841>
80. Origen, J., *et al.* Should asymptomatic bacteriuria be systematically treated in kidney transplant recipients? Results from a randomized controlled trial. *Am J Transplant*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27088545>
81. Grabe, M., *et al.* The effect of a short antibiotic course in transurethral prostatic resection. *Scand J Urol Nephrol*, 1984. 18: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/6202000>
82. Cafferkey, M.T., *et al.* Antibiotics for the prevention of septicemia in urology. *J Antimicrob Chemother*, 1982. 9: 471.
<https://www.ncbi.nlm.nih.gov/pubmed/7107549>
83. Murphy, D.M., *et al.* Bacteraemia during prostatectomy and other transurethral operations: influence of timing of antibiotic administration. *J Clin Pathol*, 1984. 37: 673.
<https://www.ncbi.nlm.nih.gov/pubmed/6725613>
84. Tencer, J. Asymptomatic bacteriuria--a long-term study. *Scand J Urol Nephrol*, 1988. 22: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/3387908>
85. Widmer, M., *et al.* Duration of treatment for asymptomatic bacteriuria during pregnancy. *Cochrane Database Syst Rev*, 2015: CD000491.
<https://www.ncbi.nlm.nih.gov/pubmed/26560337>
86. Zhanel, G.G., *et al.* Asymptomatic bacteriuria in patients with diabetes mellitus. *Rev Infect Dis*, 1991. 13: 150.
<https://www.ncbi.nlm.nih.gov/pubmed/2017615>
87. Harding, G.K., *et al.* Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engl J Med*, 2002. 347: 1576.
<https://www.ncbi.nlm.nih.gov/pubmed/12432044>
88. Mody, L., *et al.* Urinary tract infections in older women: a clinical review. *JAMA*, 2014. 311: 844.
<https://www.ncbi.nlm.nih.gov/pubmed/24570248>
89. Nicolle, L.E. Asymptomatic bacteriuria in the elderly. *Infect Dis Clin North Am*, 1997. 11: 647.
<https://www.ncbi.nlm.nih.gov/pubmed/9378928>
90. Silver, S.A., *et al.* Positive urine cultures: A major cause of inappropriate antimicrobial use in hospitals? *Can J Infect Dis Med Microbiol*, 2009. 20: 107.
<https://www.ncbi.nlm.nih.gov/pubmed/21119801>
91. Trautner, B.W. Asymptomatic bacteriuria: when the treatment is worse than the disease. *Nat Rev Urol*, 2011.
<https://www.ncbi.nlm.nih.gov/pubmed/22143416>
92. Nicolle, L.E. Urinary tract infections in patients with spinal injuries. *Current Infectious Disease Reports*, 2014. 16.
<https://www.ncbi.nlm.nih.gov/pubmed/24445675>
93. Wullt, B., *et al.* Microbial Flora in Ileal and Colonic Neobladders. *European Urology*, 2004. 45: 233.
<https://www.ncbi.nlm.nih.gov/pubmed/14734012>
94. Wullt, B., *et al.* Bladder, bowel and bugs--bacteriuria in patients with intestinal urinary diversion. *World J Urol*, 2004. 22: 186.
<https://www.ncbi.nlm.nih.gov/pubmed/15309491>
95. Darouiche, R.O., *et al.* Bacterial interference for prevention of urinary tract infection: a prospective, randomized, placebo-controlled, double-blind pilot trial. *Clin Infect Dis*, 2005. 41: 1531.
<https://www.ncbi.nlm.nih.gov/pubmed/16231269>
96. Sunden, F., *et al.* Escherichia coli 83972 Bacteriuria Protects Against Recurrent Lower Urinary Tract Infections in Patients With Incomplete Bladder Emptying. *J Urol*, 2010. 184: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/20473149>
97. Tenke, P., *et al.* European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. *Int J Antimicrob Agents*, 2008. 31 Suppl 1: S68.
<https://www.ncbi.nlm.nih.gov/pubmed/18006279>
98. Cooper, F.P., *et al.* Policies for replacing long-term indwelling urinary catheters in adults. *Cochrane Database Syst Rev*, 2016. 7: CD011115.
<https://www.ncbi.nlm.nih.gov/pubmed/27457774>
99. Dasgupta, R., *et al.* Preoperative antibiotics before endourologic surgery: current recommendations. *J Endourol*, 2009. 23: 1567.
<https://www.ncbi.nlm.nih.gov/pubmed/19785548>

100. Sobel, J.D., *et al.* Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group. *Clin Infect Dis*, 2000. 30: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/10619727>
101. Cordero-Ampuero, J., *et al.* Are antibiotics necessary in hip arthroplasty with asymptomatic bacteriuria? Seeding risk with/without treatment. *Clinical Orthopaedics and Related Research*, 2013. 471: 3822.
<https://www.ncbi.nlm.nih.gov/pubmed/23430723>
102. Sousa, R., *et al.* Is asymptomatic bacteriuria a risk factor for prosthetic joint infection? *Clinical Infectious Diseases*, 2014. 59: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/24723280>
103. Foxman, B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Dis Mon*, 2003. 49: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/12601337>
104. Naber, K.G., *et al.* Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. *Eur Urol*, 2008. 54: 1164.
<https://www.ncbi.nlm.nih.gov/pubmed/18511178>
105. Wagenlehner, F.M., *et al.* Uncomplicated urinary tract infections. *Dtsch Arztebl Int*, 2011. 108: 415.
<https://www.ncbi.nlm.nih.gov/pubmed/21776311>
106. Stamm, W.E., *et al.* Management of urinary tract infections in adults. *N Engl J Med*, 1993. 329: 1328.
<https://www.ncbi.nlm.nih.gov/pubmed/8413414>
107. Foxman, B., *et al.* Urinary tract infection among women aged 40 to 65: behavioral and sexual risk factors. *J Clin Epidemiol*, 2001. 54: 710.
<https://www.ncbi.nlm.nih.gov/pubmed/11438412>
108. Bradbury, S.M. Collection of urine specimens in general practice: to clean or not to clean? *J R Coll Gen Pract*, 1988. 38: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/3256648>
109. Lifshitz, E., *et al.* Outpatient urine culture: does collection technique matter? *Arch Intern Med*, 2000. 160: 2537.
<https://www.ncbi.nlm.nih.gov/pubmed/10979067>
110. Fihn, S.D. Clinical practice. Acute uncomplicated urinary tract infection in women. *N Engl J Med*, 2003. 349: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/12867610>
111. Foxman, B., *et al.* Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. *Infect Dis Clin North Am*, 2003. 17: 227.
<https://www.ncbi.nlm.nih.gov/pubmed/12601337>
112. Kunin, C., *Urinary tract infections*, in *Detection, prevention and management*. 1997, Lea & Febiger: Philadelphia.
113. Falagas, M.E., *et al.* Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. *J Infect*, 2009. 58: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/19195714>
114. Gupta, K., *et al.* Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med*, 2007. 167: 2207.
<https://www.ncbi.nlm.nih.gov/pubmed/17998493>
115. Lecomte, F., *et al.* Single-dose treatment of cystitis with fosfomycin trometamol (Monuril): analysis of 15 comparative trials on 2,048 patients. *Giorn It Ost Gin*, 1997. 19: 399. [No abstract available]
116. Nicolle, L.E. Pivmecillinam in the treatment of urinary tract infections. *J Antimicrob Chemother*, 2000. 46 Suppl 1: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/11051622>
117. Gupta, K., *et al.* Outcomes associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. *Int J Antimicrob Agents*, 2002. 19: 554.
<https://www.ncbi.nlm.nih.gov/pubmed/12135847>
118. Warren, J.W., *et al.* Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis*, 1999. 29: 745.
<https://www.ncbi.nlm.nih.gov/pubmed/10589881>
119. Hooton, T.M., *et al.* Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. *JAMA*, 2012. 307: 583.
<https://www.ncbi.nlm.nih.gov/pubmed/22318279>

120. Hooton, T.M., *et al.* Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. *Jama*, 2005. 293: 949.
<https://www.ncbi.nlm.nih.gov/pubmed/15728165>
121. Vazquez, J.C., *et al.* Treatments for symptomatic urinary tract infections during pregnancy. *Cochrane Database Syst Rev*, 2000: CD002256.
<https://www.ncbi.nlm.nih.gov/pubmed/10908537>
122. Wagenlehner, F.M., *et al.* Antimicrobials in urogenital infections. *Int J Antimicrob Agents*, 2011. 38 Suppl: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/22019184>
123. Nicolle, L.E., *et al.* Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis*, 2005. 40: 643.
<https://www.ncbi.nlm.nih.gov/pubmed/15714408>
124. Hooton, T.M. Recurrent urinary tract infection in women. *Int J Antimicrob Agents*, 2001. 17: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/11295405>
125. Fowler, J.E., Jr., *et al.* Excretory urography, cystography, and cystoscopy in the evaluation of women with urinary-tract infection: a prospective study. *N Engl J Med*, 1981. 304: 462.
<https://www.ncbi.nlm.nih.gov/pubmed/7453771>
126. Hooton, T.M., Prevention of recurrent urogenital tract infections in adult women, in *EAU/International Consultation on Urological Infections*. T, K.G. Naber, A.J. Schaeffer, C.F. Hynes & e. al., Editors. 2010, European Association of Urology: The Netherlands.
127. Beerepoot, M.A., *et al.* Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol*, 2013. 190: 1981.
<https://www.ncbi.nlm.nih.gov/pubmed/23867306>
128. Wagenlehner, F.M., *et al.* Prevention of recurrent urinary tract infections. *Minerva Urol Nefrol*, 2013. 65: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/23538307>
129. Raz, R., *et al.* A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med*, 1993. 329: 753.
<https://www.ncbi.nlm.nih.gov/pubmed/8350884>
130. Bauer, H.W., *et al.* Prevention of recurrent urinary tract infections with immuno-active *E. coli* fractions: a meta-analysis of five placebo-controlled double-blind studies. *Int J Antimicrob Agents*, 2002. 19: 451.
<https://www.ncbi.nlm.nih.gov/pubmed/12135831>
131. Naber, K.G., *et al.* Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. *Int J Antimicrob Agents*, 2009. 33: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/18963856>
132. Bauer, H.W., *et al.* A long-term, multicenter, double-blind study of an *Escherichia coli* extract (OM-89) in female patients with recurrent urinary tract infections. *Eur Urol*, 2005. 47: 542.
<https://www.ncbi.nlm.nih.gov/pubmed/15774256>
133. Schwenger, E.M., *et al.* Probiotics for preventing urinary tract infections in adults and children. *Cochrane Database Syst Rev*, 2015: CD008772.
<https://www.ncbi.nlm.nih.gov/pubmed/26695595>
134. Kontiokari, T., *et al.* Randomised trial of cranberry-lingonberry juice and *Lactobacillus GG* drink for the prevention of urinary tract infections in women. *Bmj*, 2001. 322: 1571.
<https://www.ncbi.nlm.nih.gov/pubmed/11431298>
135. Stothers, L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. *Can J Urol*, 2002. 9: 1558.
<https://www.ncbi.nlm.nih.gov/pubmed/12121581>
136. Jepson, R.G., *et al.* Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*, 2012. 10: CD001321.
<https://www.ncbi.nlm.nih.gov/pubmed/23076891>
137. Kranjcec, B., *et al.* D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol*, 2014. 32: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/23633128>
138. Damiano, R., *et al.* Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. *Eur Urol*, 2011. 59: 645.
<https://www.ncbi.nlm.nih.gov/pubmed/21272992>

139. Madersbacher, H., *et al.* GAG layer replenishment therapy for chronic forms of cystitis with intravesical glycosaminoglycans--a review. *Neurourol Urodyn*, 2013. 32: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/22782909>
140. Albert, X., *et al.* Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database Syst Rev*, 2004: CD001209.
<https://www.ncbi.nlm.nih.gov/pubmed/15266443>
141. Pfau, A., *et al.* Effective prophylaxis for recurrent urinary tract infections during pregnancy. *Clin Infect Dis*, 1992. 14: 810.
<https://www.ncbi.nlm.nih.gov/pubmed/1576275>
142. Schaeffer, A.J., *et al.* Efficacy and safety of self-start therapy in women with recurrent urinary tract infections. *J Urol*, 1999. 161: 207.
<https://www.ncbi.nlm.nih.gov/pubmed/10037399>
143. Scholes, D., *et al.* Risk factors associated with acute pyelonephritis in healthy women. *Ann Intern Med*, 2005. 142: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/15630106>
144. Hill, J.B., *et al.* Acute pyelonephritis in pregnancy. *Obstet Gynecol*, 2005. 105: 18.
<https://www.ncbi.nlm.nih.gov/pubmed/15625136>
145. Fulop, T. Acute Pyelonephritis Workup. 2012.
<http://emedicine.medscape.com/article/245559-workup>
146. van Nieuwkoop, C., *et al.* Predicting the need for radiologic imaging in adults with febrile urinary tract infection. *Clin Infect Dis*, 2010. 51: 1266.
<https://www.ncbi.nlm.nih.gov/pubmed/21034195>
147. Gupta, K., *et al.* International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*, 2011. 52: e103.
<https://www.ncbi.nlm.nih.gov/pubmed/21292654>
148. Hooton, T.M. Clinical practice. Uncomplicated urinary tract infection. *N Engl J Med*, 2012. 366: 1028.
<https://www.ncbi.nlm.nih.gov/pubmed/22417256>
149. Pitout, J.D. Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: changing epidemiology and drug treatment choices. *Drugs*, 2010. 70: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/20166768>
150. Mombelli, G., *et al.* Oral vs intravenous ciprofloxacin in the initial empirical management of severe pyelonephritis or complicated urinary tract infections: a prospective randomized clinical trial. *Arch Intern Med*, 1999. 159: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/9892331>
151. Millar, L.K., *et al.* Outpatient treatment of pyelonephritis in pregnancy: a randomized controlled trial. *Obstet Gynecol*, 1995. 86: 560.
<https://www.ncbi.nlm.nih.gov/pubmed/7675380>
152. Wing, D.A., *et al.* A randomized trial of three antibiotic regimens for the treatment of pyelonephritis in pregnancy. *Obstet Gynecol*, 1998. 92: 249.
<https://www.ncbi.nlm.nih.gov/pubmed/9699761>
153. Ulleryd, P., *et al.* Ciprofloxacin for 2 or 4 weeks in the treatment of febrile urinary tract infection in men: a randomized trial with a 1 year follow-up. *Scand J Infect Dis*, 2003. 35: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/12685882>
154. Reyner, K., *et al.* Urinary obstruction is an important complicating factor in patients with septic shock due to urinary infection. *Am J Emerg Med*, 2016. 34: 694.
<https://www.ncbi.nlm.nih.gov/pubmed/26905806>
155. Heyns, C.F. Urinary tract infection associated with conditions causing urinary tract obstruction and stasis, excluding urolithiasis and neuropathic bladder. *World J Urol*, 2012. 30: 77.
<https://www.ncbi.nlm.nih.gov/pubmed/21720861>
156. Spoorenberg, V., *et al.* [Better antibiotic use in complicated urinary tract infections; multicentre cluster randomised trial of 2 improvement strategies]. *Ned Tijdschr Geneesk*, 2016. 160: D460.
<https://www.ncbi.nlm.nih.gov/pubmed/27438395>
157. Geerlings, S.E., *et al.* SWAB Guidelines for Antimicrobial Therapy of Complicated Urinary Tract Infections in Adults. *SWAB Guidelines*, 2013.
<https://www.ncbi.nlm.nih.gov/pubmed/17100128>

158. Hooton, T.M., *et al.* Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*, 2010. 50: 625.
<https://www.ncbi.nlm.nih.gov/pubmed/20175247>
159. Peterson, J., *et al.* Identification and pretherapy susceptibility of pathogens in patients with complicated urinary tract infection or acute pyelonephritis enrolled in a clinical study in the United States from November 2004 through April 2006. *Clin Ther*, 2007. 29: 2215.
<https://www.ncbi.nlm.nih.gov/pubmed/18042477>
160. Bader, M.S., *et al.* Management of complicated urinary tract infections in the era of antimicrobial resistance. *Postgrad Med*, 2010. 122: 7.
<https://www.ncbi.nlm.nih.gov/pubmed/21084776>
161. Wagenlehner, F., *et al.* The Global Prevalence of Infections in Urology Study: A Long-Term, Worldwide Surveillance Study on Urological Infections. *Pathogens*, 2016. 5.
<https://www.ncbi.nlm.nih.gov/pubmed/26797640>
162. van der Starre, W.E., *et al.* Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection. *J Antimicrob Chemother*, 2011. 66: 650.
<https://www.ncbi.nlm.nih.gov/pubmed/21123286>
163. Gould, C.V., *et al.* Guideline for prevention of catheter-associated urinary tract infections 2009. *Infect Control Hosp Epidemiol*, 2010. 31: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/20156062>
164. Garibaldi, R.A., *et al.* Factors predisposing to bacteriuria during indwelling urethral catheterization. *N Engl J Med*, 1974. 291: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/4834750>
165. Kunin, C.M., *et al.* Prevention of catheter-induced urinary-tract infections by sterile closed drainage. *N Engl J Med*, 1966. 274: 1155.
<https://www.ncbi.nlm.nih.gov/pubmed/5934951>
166. Hartstein, A.I., *et al.* Nosocomial urinary tract infection: a prospective evaluation of 108 catheterized patients. *Infect Control*, 1981. 2: 380.
<https://www.ncbi.nlm.nih.gov/pubmed/6795141>
167. Warren, J.W., *et al.* Fever, bacteremia, and death as complications of bacteriuria in women with long-term urethral catheters. *J Infect Dis*, 1987. 155: 1151.
<https://www.ncbi.nlm.nih.gov/pubmed/3572035>
168. Classen, D.C., *et al.* Prevention of catheter-associated bacteriuria: clinical trial of methods to block three known pathways of infection. *Am J Infect Control*, 1991. 19: 136.
<https://www.ncbi.nlm.nih.gov/pubmed/1863002>
169. Saint, S., *et al.* Preventing catheter-related bacteriuria: should we? Can we? How? *Arch Intern Med*, 1999. 159: 800.
<https://www.ncbi.nlm.nih.gov/pubmed/10219925>
170. Maki, D.G., *et al.* Engineering out the risk for infection with urinary catheters. *Emerg Infect Dis*, 2001. 7: 342.
<https://www.ncbi.nlm.nih.gov/pubmed/11294737>
171. Jacobsen, S.M., *et al.* Complicated catheter-associated urinary tract infections due to *Escherichia coli* and *Proteus mirabilis*. *Clin Microbiol Rev*, 2008. 21: 26.
<https://www.ncbi.nlm.nih.gov/pubmed/18202436>
172. Dellinger, R.P., *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*, 2013. 39: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/15090974>
173. Martin, G.S., *et al.* The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*, 2003. 348: 1546.
<https://www.ncbi.nlm.nih.gov/pubmed/12700374>
174. Hotchkiss, R.S., *et al.* The pathophysiology and treatment of sepsis. *N Engl J Med*, 2003. 348: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/12519925>
175. Rosser, C.J., *et al.* Urinary tract infections in the critically ill patient with a urinary catheter. *Am J Surg*, 1999. 177: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/10326844>
176. Brun-Buisson, C., *et al.* EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med*, 2004. 30: 580.
<https://www.ncbi.nlm.nih.gov/pubmed/14997295>

177. Cek, M., *et al.* Healthcare-associated urinary tract infections in hospitalized urological patients--a global perspective: results from the GPIU studies 2003-2010. *World J Urol*, 2014. 32: 1587.
<https://www.ncbi.nlm.nih.gov/pubmed/24452449>
178. Tandogdu, Z., *et al.* Antimicrobial resistance in urosepsis: outcomes from the multinational, multicenter global prevalence of infections in urology (GPIU) study 2003-2013. *World J Urol*, 2016. 34: 1193.
<https://www.ncbi.nlm.nih.gov/pubmed/26658886>
179. Bone, R.C., *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*, 1992. 101: 1644.
<https://www.ncbi.nlm.nih.gov/pubmed/1303622>
180. Levy, M.M., *et al.* 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*, 2003. 31: 1250.
<https://www.ncbi.nlm.nih.gov/pubmed/12682500>
181. Singer, M., *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, 2016. 315: 801.
<https://www.ncbi.nlm.nih.gov/pubmed/26903338>
182. Brunkhorst, F.M., *et al.* Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Med*, 2000. 26 Suppl 2: S148.
<https://www.ncbi.nlm.nih.gov/pubmed/18470710>
183. Angeletti, S., *et al.* Procalcitonin, MR-Proadrenomedullin, and Cytokines Measurement in Sepsis Diagnosis: Advantages from Test Combination. *Dis Markers*, 2015. 2015: 951532.
<https://www.ncbi.nlm.nih.gov/pubmed/26635427>
184. Harbarth, S., *et al.* Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med*, 2001. 164: 396.
<https://www.ncbi.nlm.nih.gov/pubmed/11500339>
185. Mikkelsen, M.E., *et al.* Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med*, 2009. 37: 1670.
<https://www.ncbi.nlm.nih.gov/pubmed/19325467>
186. Carlet, J., *et al.* Guidelines for prevention of nosocomial infections in intensive care unit. *Arnette Ed Paris 1994*: 41. [No abstract available]
187. Riedl, C.R., *et al.* Bacterial colonization of ureteral stents. *Eur Urol*, 1999. 36: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/10364656>
188. DeGroot-Kosolcharoen, J., *et al.* Evaluation of a urinary catheter with a preconnected closed drainage bag. *Infect Control Hosp Epidemiol*, 1988. 9: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/3343502>
189. Rivers, E., *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*, 2001. 345: 1368.
<https://www.ncbi.nlm.nih.gov/pubmed/11794169>
190. Mouncey, P.R., *et al.* Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*, 2015. 372: 1301.
<https://www.ncbi.nlm.nih.gov/pubmed/25776532>
191. ARISE Investigators. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*, 2014. 371: 1496.
<https://www.ncbi.nlm.nih.gov/pubmed/25272316>
192. ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*, 2014. 370: 1683.
<https://www.ncbi.nlm.nih.gov/pubmed/24635773>
193. Dellinger, R.P., *et al.* Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*, 2004. 32: 858.
<https://www.ncbi.nlm.nih.gov/pubmed/15090974>
194. Centers for Disease Control and Prevention (CDC) 2010 STD Treatment Guidelines.
<https://www.cdc.gov/std/treatment/2010/std-treatment-2010-rr5912.pdf>
195. Del Rio, C., *et al.* Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral cephalosporins no longer a recommended treatment for gonococcal infections. *MMWR*, 2012. 61: 590.
<https://www.ncbi.nlm.nih.gov/pubmed/22874837>
196. Bremer, V., *et al.* Gonorrhoea in adults and adolescents AWMF S2k guidelines. 2013. Nr. 059/004.
<http://www.egms.de/static/en/journals/id/2014-2/id000010.shtml>

197. Plettenberg, A. STI – Sexually transmitted infections. ifi, 2014.
<http://app.ifi-medizin.de/sti/>
198. Wetmore, C.M., *et al.* Demographic, behavioral, and clinical characteristics of men with nongonococcal urethritis differ by etiology: a case-comparison study. *Sex Transm Dis*, 2011. 38: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/21285914>
199. Borchardt, K.A., *et al.* Prevalence of *Trichomonas vaginalis* in a male sexually transmitted disease clinic population by interview, wet mount microscopy, and the InPouch TV test. *Genitourin Med*, 1995. 71: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/8566985>
200. Busolo, F., *et al.* Detection of *Mycoplasma genitalium* and *Chlamydia trachomatis* DNAs in male patients with urethritis using the polymerase chain reaction. *New Microbiol*, 1997. 20: 325.
<https://www.ncbi.nlm.nih.gov/pubmed/9385602>
201. Evans, B.A., *et al.* Racial origin, sexual behaviour, and genital infection among heterosexual men attending a genitourinary medicine clinic in London (1993-4). *Sex Transm Infect*, 1998. 74: 40.
<https://www.ncbi.nlm.nih.gov/pubmed/9634302>
202. Evans, B.A., *et al.* Racial origin, sexual lifestyle, and genital infection among women attending a genitourinary medicine clinic in London (1992). *Sex Transm Infect*, 1998. 74: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/9634303>
203. Krieger, J.N. Trichomoniasis in men: old issues and new data. *Sex Transm Dis*, 1995. 22: 83.
<https://www.ncbi.nlm.nih.gov/pubmed/7624817>
204. Ito, S., *et al.* Male non-gonococcal urethritis: From microbiological etiologies to demographic and clinical features. *Int J Urol*, 2016. 23: 325.
<https://www.ncbi.nlm.nih.gov/pubmed/26845624>
205. You, C., *et al.* The first report: An analysis of bacterial flora of the first voided urine specimens of patients with male urethritis using the 16S ribosomal RNA gene-based clone library method. *Microb Pathog*, 2016. 95: 95.
<https://www.ncbi.nlm.nih.gov/pubmed/27013259>
206. Haggerty, C.L., *et al.* Risk of sequelae after *Chlamydia trachomatis* genital infection in women. *J Infect Dis*, 2010. 201 Suppl 2: S134.
<https://www.ncbi.nlm.nih.gov/pubmed/20470050>
207. Witkin, S.S., *et al.* Detection of *Chlamydia trachomatis* by the polymerase chain reaction in the cervixes of women with acute salpingitis. *Am J Obstet Gynecol*, 1993. 168: 1438.
<https://www.ncbi.nlm.nih.gov/pubmed/8498424>
208. Workowski, K.A., *et al.* Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*, 2015. 64: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/26042815>
209. Swartz, S.L., *et al.* Diagnosis and etiology of nongonococcal urethritis. *J Infect Dis*, 1978. 138: 445.
<https://www.ncbi.nlm.nih.gov/pubmed/213495>
210. Papp, J.R., *et al.* Recommendations for the Laboratory-Based Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* — 2014. Recommendations and reports : Morbidity and mortality weekly report. Centers for Disease Control, 2014. 63: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/24622331>
211. Kirkcaldy, R.D., *et al.* *Neisseria gonorrhoeae* Antimicrobial Susceptibility Surveillance - The Gonococcal Isolate Surveillance Project, 27 Sites, United States, 2014. *MMWR Surveill Summ*, 2016. 65: 1.
<https://www.cdc.gov/mmwr/volumes/65/ss/ss6507a1.htm>
212. Yuan, Z., *et al.* Randomized controlled clinical trial on the efficacy of fosfomycin trometamol for uncomplicated gonococcal urethritis in men. *Clin Microbiol Infect*, 2016. 22: 507.
<https://www.ncbi.nlm.nih.gov/pubmed/27064136>
213. Alexander, R.B., *et al.* Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis/chronic pelvic pain syndrome. *Urology*, 1998. 52: 744.
<https://www.ncbi.nlm.nih.gov/pubmed/9801092>
214. Alexander, R.B., *et al.* Chronic prostatitis: results of an Internet survey. *Urology*, 1996. 48: 568.
<https://www.ncbi.nlm.nih.gov/pubmed/8886062>
215. Zermann, D.H., *et al.* Neurourological insights into the etiology of genitourinary pain in men. *J Urol*, 1999. 161: 903.
<https://www.ncbi.nlm.nih.gov/pubmed/10022711>

216. Weidner, W., *et al.* Chronic prostatitis: a thorough search for etiologically involved microorganisms in 1,461 patients. *Infection*, 1991. 19 Suppl 3: S119.
<https://www.ncbi.nlm.nih.gov/pubmed/2055646>
217. Meares, E.M., *et al.* Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol*, 1968. 5: 492.
<https://www.ncbi.nlm.nih.gov/pubmed/4870505>
218. Gill, B.C., *et al.* Bacterial prostatitis. *Curr Opin Infect Dis*, 2016. 29: 86.
<https://www.ncbi.nlm.nih.gov/pubmed/26555038>
219. Wagenlehner, F.M., *et al.* Prostatitis: the role of antibiotic treatment. *World J Urol*, 2003. 21: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/12687400>
220. Schneider, H., *et al.* The 2001 Giessen Cohort Study on patients with prostatitis syndrome--an evaluation of inflammatory status and search for microorganisms 10 years after a first analysis. *Andrologia*, 2003. 35: 258.
<https://www.ncbi.nlm.nih.gov/pubmed/14535851>
221. Naber, K.G., *et al.*, Prostatitis, epididymitis and orchitis, in *Infectious diseases*, D. Armstrong & J. Cohen, Editors. 1999, Mosby: London.
222. Badalyan, R.R., *et al.* Chlamydial and ureaplasma infections in patients with nonbacterial chronic prostatitis. *Andrologia*, 2003. 35: 263.
<https://www.ncbi.nlm.nih.gov/pubmed/14535852>
223. Berger, R.E., Epididymitis., in *Sexually transmitted diseases*, K.K. Holmes, P.-A. Mardh, P.F. Sparling & P.J. Wiesner, Editors. 1984, McGraw-Hill: New York.
224. Robinson, A.J., *et al.* Acute epididymitis: why patient and consort must be investigated. *Br J Urol*, 1990. 66: 642.
<https://www.ncbi.nlm.nih.gov/pubmed/2265337>
225. Schaeffer, A.J. Prostatitis: US perspective. *Int J Antimicrob Agents*, 1999. 11: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/10394972>
226. Krieger, J.N., *et al.* NIH consensus definition and classification of prostatitis. *Jama*, 1999. 282: 236.
<https://www.ncbi.nlm.nih.gov/pubmed/10422990>
227. Workshop Committee of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). Chronic prostatitis workshop. 1995: Bethesda, Maryland.
<http://jac.oxfordjournals.org/content/46/2/157.full>
228. Krieger, J.N. Recurrent lower urinary tract infections in men. *J New Rem Clin*, 1998. 47: 4. [No abstract available]
229. Krieger, J.N., *et al.* Chronic pelvic pains represent the most prominent urogenital symptoms of "chronic prostatitis". *Urology*, 1996. 48: 715.
<https://www.ncbi.nlm.nih.gov/pubmed/8911515>
230. Nickel, J.C. Effective office management of chronic prostatitis. *Urol Clin North Am*, 1998. 25: 677.
<https://www.ncbi.nlm.nih.gov/pubmed/10026774>
231. Litwin, M.S., *et al.* The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol*, 1999. 162: 369.
<https://www.ncbi.nlm.nih.gov/pubmed/10411041>
232. Wagenlehner, F.M., *et al.* Bacterial prostatitis. *World J Urol*, 2013. 31: 711.
<https://www.ncbi.nlm.nih.gov/pubmed/23519458>
233. Doble, A., *et al.* Ultrasonographic findings in prostatitis. *Urol Clin North Am*, 1989. 16: 763.
<https://www.ncbi.nlm.nih.gov/pubmed/2683305>
234. Bozeman, C.B., *et al.* Treatment of chronic prostatitis lowers serum prostate specific antigen. *J Urol*, 2002. 167: 1723.
<https://www.ncbi.nlm.nih.gov/pubmed/11912396>
235. Polascik, T.J., *et al.* Prostate specific antigen: a decade of discovery--what we have learned and where we are going. *J Urol*, 1999. 162: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/10411025>
236. Schaeffer, A.J., *et al.* Summary consensus statement: diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome. *Eur Urol* 2003. 43: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/12521576>
237. Bjerklund Johansen, T.E., *et al.* The role of antibiotics in the treatment of chronic prostatitis: a consensus statement. *Eur Urol*, 1998. 34: 457.
<https://www.ncbi.nlm.nih.gov/pubmed/9831786>
238. Naber, K.G. Antimicrobial Treatment of Bacterial Prostatitis. *Eur Urol Suppl*, 2003. 2: 23.
<http://www.sciencedirect.com/science/article/pii/S1569905602001963>

239. Ohkawa, M., *et al.* Antimicrobial treatment for chronic prostatitis as a means of defining the role of *Ureaplasma urealyticum*. *Urol Int*, 1993. 51: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/8249222>
240. Jimenez-Cruz, J.F., *et al.* Treatment of chronic prostatitis: intraprostatic antibiotic injections under echography control. *J Urol*, 1988. 139: 967.
<https://www.ncbi.nlm.nih.gov/pubmed/3283385>
241. Mayersak, J.S. Transrectal ultrasonography directed intraprostatic injection of gentamycin-xylocaine in the management of the benign painful prostate syndrome. A report of a 5 year clinical study of 75 patients. *Int Surg*, 1998. 83: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/10096759>
242. Hua, L.X., *et al.* [The diagnosis and treatment of acute prostatitis: report of 35 cases]. *Zhonghua Nan Ke Xue*, 2005. 11: 897.
<https://www.ncbi.nlm.nih.gov/pubmed/16398358>
243. Yoon, B.I., *et al.* Acute bacterial prostatitis: how to prevent and manage chronic infection? *J Infect Chemother*, 2012. 18: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/22215226>
244. Ludwig, M., *et al.* Diagnosis and therapeutic management of 18 patients with prostatic abscess. *Urology*, 1999. 53: 340.
<https://www.ncbi.nlm.nih.gov/pubmed/9933051>
245. Chou, Y.H., *et al.* Prostatic abscess: transrectal color Doppler ultrasonic diagnosis and minimally invasive therapeutic management. *Ultrasound Med Biol*, 2004. 30: 719.
<https://www.ncbi.nlm.nih.gov/pubmed/15219951>
246. Çek, M., *et al.* Acute and Chronic Epididymitis in EAU-EBU Update Series. *Eur Urol Suppl* 2015. (in press). [No abstract available]
247. Harnisch, J.P., *et al.* Aetiology of acute epididymitis. *Lancet*, 1977. 1: 819.
<https://www.ncbi.nlm.nih.gov/pubmed/67333>
248. Abbara, A., *et al.* Etiology and management of genitourinary tuberculosis. *Nat Rev Urol*, 2011. 8: 678.
<https://www.ncbi.nlm.nih.gov/pubmed/22157940>
249. Street, E., *et al.* IUSTI EO Guideline on the management of epididymo-orchitis. 2012.
http://www.iusti.org/regions/europe/pdf/2013/Epididymo-orchitis-2013IUSTI_WHO.pdf
250. Street, E., *et al.* BASHH 2010 United Kingdom national guideline for the management of epididymo-orchitis. 2010.
<http://www.bashh.org/documents/3546.pdf>
251. Majumdar, R., *et al.* Prostate laser vaporization is safe and effective in elderly men. *Urology Annals*, 2015. 7: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/25657541>
252. Banyra, O., *et al.* Acute epididymo-orchitis: staging and treatment. *Cent European J Urol*, 2012. 65: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/24578950>
253. Haddadeen, C., *et al.* Comparative regional audit of urology and genito-urinary departments in the management of acute epididymo-orchitis. *HIV Medicine*, 2010. 11: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/70186144>
254. Nicholson, A., *et al.* Management of epididymo-orchitis in primary care: Results from a large UK primary care database. *Brit J Gen Pract*, 2010. 60: e407.
<https://www.ncbi.nlm.nih.gov/pubmed/20883615>
255. Pilatz, A., *et al.* Impact of bacterial epididymitis on semen quality after antibiotic treatment. *J Urol*, 2012. 1): e443.
<https://www.ncbi.nlm.nih.gov/pubmed/70720788>
256. Pilatz, A., *et al.* Acute Epididymitis Revisited: Impact of Molecular Diagnostics on Etiology and Contemporary Guideline Recommendations. *Eur Urol*, 2015. 68: 428.
<https://www.ncbi.nlm.nih.gov/pubmed/25542628>
257. Smith, G.L., *et al.* Fournier's gangrene. *Br J Urol*, 1998. 81: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/9523650>
258. Thwaini, A., *et al.* Fournier's gangrene and its emergency management. *Postgrad Med J*, 2006. 82: 516.
<https://www.ncbi.nlm.nih.gov/pubmed/16891442>
259. Morpurgo, E., *et al.* Fournier's gangrene. *Surg Clin North Am*, 2002. 82: 1213.
<https://www.ncbi.nlm.nih.gov/pubmed/12516849>

260. Eke, N. Fournier's gangrene: a review of 1726 cases. *Br J Surg*, 2000. 87: 718.
<https://www.ncbi.nlm.nih.gov/pubmed/10848848>
261. Ferreira, P.C., *et al.* Fournier's gangrene: a review of 43 reconstructive cases. *Plast Reconstr Surg*, 2007. 119: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/17255671>
262. Paty, R., *et al.* Gangrene and Fournier's gangrene. *Urol Clin North Am*, 1992. 19: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/1736475>
263. Sorensen, M.D., *et al.* Fournier's gangrene: management and mortality predictors in a population based study. *J Urol*, 2009. 182: 2742.
<https://www.ncbi.nlm.nih.gov/pubmed/19837424>
264. Janane, A., *et al.* [Hyperbaric oxygen therapy adjunctive to surgical debridement in management of Fournier's gangrene: usefulness of a severity index score in predicting disease gravity and patient survival]. *Actas Urol Esp*, 2011. 35: 332.
<https://www.ncbi.nlm.nih.gov/pubmed/21496959>
265. Tuncel, A., *et al.* Fournier's gangrene: Three years of experience with 20 patients and validity of the Fournier's Gangrene Severity Index Score. *Eur Urol*, 2006. 50: 838.
<https://www.ncbi.nlm.nih.gov/pubmed/16513250>
266. Wong, C.H., *et al.* The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med*, 2004. 32: 1535.
<https://www.ncbi.nlm.nih.gov/pubmed/15241098>
267. Chennamsetty, A., *et al.* Contemporary diagnosis and management of Fournier's gangrene. *Ther Adv Urol*, 2015. 7: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/26445600>
268. Proud, D., *et al.* Are we getting necrotizing soft tissue infections right? A 10-year review. *ANZ J Surg*, 2014. 84: 468.
<https://www.ncbi.nlm.nih.gov/pubmed/24164901>
269. Jallali, N., *et al.* Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. *Am J Surg*, 2005. 189: 462.
<https://www.ncbi.nlm.nih.gov/pubmed/15820462>
270. Mallikarjuna, M.N., *et al.* Fournier's Gangrene: Current Practices. *ISRN Surg*, 2012. 2012: 942437.
<https://www.ncbi.nlm.nih.gov/pubmed/23251819>
271. Singh, A., *et al.* Fournier's gangrene. A clinical review. *Arch Ital Urol Androl*, 2016. 88: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/27711086>
272. Erol, B., *et al.* Fournier's gangrene: overview of prognostic factors and definition of new prognostic parameter. *Urology*, 2010. 75: 1193.
<https://www.ncbi.nlm.nih.gov/pubmed/20451745>
273. Ozturk, E., *et al.* What are the indications for a stoma in Fournier's gangrene? *Colorectal Dis*, 2011. 13: 1044.
<https://www.ncbi.nlm.nih.gov/pubmed/20579084>
274. Roghmann, F., *et al.* Is there a need for the Fournier's gangrene severity index? Comparison of scoring systems for outcome prediction in patients with Fournier's gangrene. *BJU Int*, 2012. 110: 1359.
<https://www.ncbi.nlm.nih.gov/pubmed/22494217>
275. Sarani, B., *et al.* Necrotizing fasciitis: current concepts and review of the literature. *J Am Coll Surg*, 2009. 208: 279.
<https://www.ncbi.nlm.nih.gov/pubmed/19228540>
276. Aigere, E.O., *et al.* Enhanced urinalysis in the detection of asymptomatic bacteriuria in pregnancy. *Nig Q J Hosp Med*, 2013. 23: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/24579505>
277. Ajayi, A.B., *et al.* Reliability of urine multistix and gram stain in the detection of asymptomatic bacteriuria in pregnancy. *West Afr J Med*, 2010. 29: 339.
<https://www.ncbi.nlm.nih.gov/pubmed/21089022>
278. Al-Daghistani, H.I., *et al.* Diagnostic value of various urine tests in the Jordanian population with urinary tract infection. *Clin Chem Lab Med*, 2002. 40: 1048.
<https://www.ncbi.nlm.nih.gov/pubmed/12476947>
279. Buchsbaum, G.M., *et al.* Utility of urine reagent strip in screening women with incontinence for urinary tract infection. *Int Urogynecol J Pelvic Floor Dysfunct*, 2004. 15: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/15278254>

280. D'Souza, H.A., *et al.* Practical bench comparison of BBL CHROMagar Orientation and standard two-plate media for urine cultures. *J Clin Microbiol*, 2004. 42: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/14715732>
281. Demilie, T., *et al.* Diagnostic accuracy of rapid urine dipstick test to predict urinary tract infection among pregnant women in Felege Hiwot Referral Hospital, Bahir Dar, North West Ethiopia. *BMC Res Notes*, 2014. 7: 481.
<https://www.ncbi.nlm.nih.gov/pubmed/25073620>
282. Honey, R.J., *et al.* A prospective study examining the incidence of bacteriuria and urinary tract infection after shock wave lithotripsy with targeted antibiotic prophylaxis. *J Urol*, 2013. 189: 2112.
<https://www.ncbi.nlm.nih.gov/pubmed/23276509>
283. Arinzon, Z., *et al.* Detection of urinary tract infection (UTI) in long-term care setting: Is the multireagent strip an adequate diagnostic tool? *Arch Gerontol Geriatr*, 2009. 48: 227.
<https://www.ncbi.nlm.nih.gov/pubmed/18314207>
284. Eigbefoh, J.O., *et al.* The diagnostic accuracy of the rapid dipstick test to predict asymptomatic urinary tract infection of pregnancy. *J Obstet Gynaecol*, 2008. 28: 490.
<https://www.ncbi.nlm.nih.gov/pubmed/18850421>
285. Falbo, R., *et al.* Bacteriuria screening by automated whole-field-image-based microscopy reduces the number of necessary urine cultures. *J Clin Microbiol*, 2012. 50: 1427.
<https://www.ncbi.nlm.nih.gov/pubmed/22238436>
286. Greeff, A., *et al.* Uricult Trio as a screening test for bacteriuria in pregnancy. *S Afr Med J*, 2002. 92: 306.
<https://www.ncbi.nlm.nih.gov/pubmed/12056364>
287. Khasriya, R., *et al.* The inadequacy of urinary dipstick and microscopy as surrogate markers of urinary tract infection in urological outpatients with lower urinary tract symptoms without acute frequency and dysuria. *J Urol*, 2010. 183: 1843.
<https://www.ncbi.nlm.nih.gov/pubmed/20303096>
288. Koeijers, J.J., *et al.* Evaluation of the nitrite and leukocyte esterase activity tests for the diagnosis of acute symptomatic urinary tract infection in men. *Clin Infect Dis*, 2007. 45: 894.
<https://www.ncbi.nlm.nih.gov/pubmed/17806056>
289. Lammers, R.L., *et al.* Comparison of test characteristics of urine dipstick and urinalysis at various test cutoff points. *Ann Emerg Med*, 2001. 38: 505.
<https://www.ncbi.nlm.nih.gov/pubmed/11679861>
290. Mignini, L., *et al.* Accuracy of diagnostic tests to detect asymptomatic bacteriuria during pregnancy. *Obstet Gynecol*, 2009. 113: 346.
<https://www.ncbi.nlm.nih.gov/pubmed/19155905>
291. Millar, L., *et al.* Rapid enzymatic urine screening test to detect bacteriuria in pregnancy. *Obstet Gynecol*, 2000. 95: 601.
<https://www.ncbi.nlm.nih.gov/pubmed/10725497>
292. Panagamuwa, C., *et al.* Dipstick screening for urinary tract infection before arthroplasty: a safe alternative to laboratory testing? *Int J Clin Pract*, 2004. 58: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/14994965>
293. Raza-Khan, F., *et al.* Usefulness of urine dipstick in an urogynecologic population. *Int Urogynecol J Pelvic Floor Dysfunct*, 2006. 17: 489.
<https://www.ncbi.nlm.nih.gov/pubmed/16408149>
294. Shang, Y., *et al.* Systematic review and meta-analysis of flow cytometry in urinary tract infection screening. *Clinica Chimica Acta*, 2013. 424.
<https://www.ncbi.nlm.nih.gov/pubmed/23721948>
295. Horan, T.C., *et al.*, Surveillance of nosocomial infections, in *Hospital epidemiology and infection control*, M. CG, Editor. 2004, Lippincott, Williams & Wilkins: Philadelphia.
296. Bjerklund Johansen, T.E., *et al.* Prevalence of hospital-acquired urinary tract infections in urology departments. *Eur Urol*, 2007. 51: 1100.
<https://www.ncbi.nlm.nih.gov/pubmed/17049419>
297. Grabe, M. Controversies in antibiotic prophylaxis in urology. *Int J Antimicrob Agents*, 2004. 23 Suppl 1: S17.
<https://www.ncbi.nlm.nih.gov/pubmed/15037324>
298. Cruse, P.J., *et al.* The epidemiology of wound infection. A 10-year prospective study of 62,939 wounds. *Surg Clin North Am*, 1980. 60: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/7361226>

299. American Society of Health-System Pharmacists. Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery. ASHP Therapeutic Guidelines, 2013.
<http://www.ashp.org/surgical-guidelines>
300. Zweigner, J., *et al.* Systematic review and evidencebased guidance on perioperative antibiotic prophylaxis. ECDC Technical Report, 2015.
<http://ecdc.europa.eu/en/publications/Publications/Perioperative%20antibiotic%20prophylaxis%20-%20June%202013.pdf>
301. Garcia-Perdomo, H.A., *et al.* Efficacy of antibiotic prophylaxis in patients undergoing cystoscopy: a randomized clinical trial. *World J Urol*, 2013. 31: 1433.
<https://www.ncbi.nlm.nih.gov/pubmed/23412704>
302. Herr, H.W. Should antibiotics be given prior to outpatient cystoscopy? A plea to urologists to practice antibiotic stewardship. *Eur Urol*, 2014. 65: 839.
<https://www.ncbi.nlm.nih.gov/pubmed/24012206>
303. Alsaywid, B.S., *et al.* Antibiotic prophylaxis for transurethral urological surgeries: Systematic review. *Urol Ann*, 2013. 5: 61.
<https://www.ncbi.nlm.nih.gov/pubmed/23798859>
304. Almallah, Y.Z., *et al.* Urinary tract infection and patient satisfaction after flexible cystoscopy and urodynamic evaluation. *Urology*, 2000. 56: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/10869618>
305. Burke, D.M., *et al.* The community-based morbidity of flexible cystoscopy. *BJU Int*, 2002. 89: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/11872022>
306. Clark, K.R., *et al.* Urinary infection following out-patient flexible cystoscopy. *Br J Urol*, 1990. 66: 503.
<https://www.ncbi.nlm.nih.gov/pubmed/2249120>
307. Cundiff, G.W., *et al.* Randomized trial of antibiotic prophylaxis for combined urodynamics and cystourethroscopy. *Obstet Gynecol*, 1999. 93: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/10912979>
308. Jimenez Cruz, J.F., *et al.* [Antimicrobial prophylaxis in urethroscopy. Comparative study]. *Actas Urol Esp*, 1993. 17: 172.
<https://www.ncbi.nlm.nih.gov/pubmed/8506770>
309. Johnson, M.I., *et al.* Oral ciprofloxacin or trimethoprim reduces bacteriuria after flexible cystoscopy. *BJU Int*, 2007. 100: 826.
<https://www.ncbi.nlm.nih.gov/pubmed/17822463>
310. Karmouni, T., *et al.* [Role of antibiotic prophylaxis in ambulatory cystoscopy]. *Prog Urol*, 2001. 11: 1239.
<https://www.ncbi.nlm.nih.gov/pubmed/11859658>
311. Latthe, P.M., *et al.* Prophylactic antibiotics in urodynamics: a systematic review of effectiveness and safety. *Neurourol Urodyn*, 2008. 27: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/17849482>
312. Logadottir, Y., *et al.* Invasive urodynamic studies are well tolerated by the patients and associated with a low risk of urinary tract infection. *Scand J Urol Nephrol*, 2001. 35: 459.
<https://www.ncbi.nlm.nih.gov/pubmed/11848424>
313. MacDermott, J.P., *et al.* Cephadrine prophylaxis in transurethral procedures for carcinoma of the bladder. *Br J Urol*, 1988. 62: 136.
<https://www.ncbi.nlm.nih.gov/pubmed/3044484>
314. Manson, A.L. Is antibiotic administration indicated after outpatient cystoscopy. *J Urol*, 1988. 140: 316.
<https://www.ncbi.nlm.nih.gov/pubmed/3398127>
315. Rane, A., *et al.* The issue of prophylactic antibiotics prior to flexible cystoscopy. *Eur Urol*, 2001. 39: 212.
<https://www.ncbi.nlm.nih.gov/pubmed/11223682>
316. Tsugawa, M., *et al.* Prospective randomized comparative study of antibiotic prophylaxis in urethroscopy and urethrocytography. *Int J Urol*, 1998. 5: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/9781431>
317. Wilson, L., *et al.* Is antibiotic prophylaxis required for flexible cystoscopy? A truncated randomized double-blind controlled trial. *J Endourol*, 2005. 19: 1006.
<https://www.ncbi.nlm.nih.gov/pubmed/16253070>

318. Wagenlehner, F.M., *et al.* Prospective, randomized, multicentric, open, comparative study on the efficacy of a prophylactic single dose of 500 mg levofloxacin versus 1920 mg trimethoprim/sulfamethoxazole versus a control group in patients undergoing TUR of the prostate. *Eur Urol*, 2005. 47: 549.
<https://www.ncbi.nlm.nih.gov/pubmed/15774257>
319. Berry, A., *et al.* Prophylactic antibiotic use in transurethral prostatic resection: a meta-analysis. *J Urol*, 2002. 167: 571.
<https://www.ncbi.nlm.nih.gov/pubmed/11792921>
320. Qiang, W., *et al.* Antibiotic prophylaxis for transurethral prostatic resection in men with preoperative urine containing less than 100,000 bacteria per ml: a systematic review. *J Urol*, 2005. 173: 1175.
<https://www.ncbi.nlm.nih.gov/pubmed/15758736>
321. Martov, A., *et al.* Postoperative infection rates in patients with a negative baseline urine culture undergoing ureteroscopic stone removal: a matched case-control analysis on antibiotic prophylaxis from the CROES URS global study. *J Endourol*, 2015. 29: 171.
<https://www.ncbi.nlm.nih.gov/pubmed/25072350>
322. Charton, M., *et al.* Urinary tract infection in percutaneous surgery for renal calculi. *J Urol*, 1986. 135: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/3510316>
323. Dogan, H.S., *et al.* Antibiotic prophylaxis in percutaneous nephrolithotomy: prospective study in 81 patients. *J Endourol*, 2002. 16: 649.
<https://www.ncbi.nlm.nih.gov/pubmed/12490017>
324. Fourcade, R.O. Antibiotic prophylaxis with cefotaxime in endoscopic extraction of upper urinary tract stones: a randomized study. The Cefotaxime Cooperative Group. *J Antimicrob Chemother*, 1990. 26 Suppl A: 77.
<https://www.ncbi.nlm.nih.gov/pubmed/2228847>
325. Hendrikx, A.J., *et al.* Treatment for extended-mid and distal ureteral stones: SWL or ureteroscopy? Results of a multicenter study. *J Endourol*, 1999. 13: 727.
<https://www.ncbi.nlm.nih.gov/pubmed/10646679>
326. Knopf, H.J., *et al.* Perioperative antibiotic prophylaxis in ureteroscopic stone removal. *Eur Urol*, 2003. 44: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/12814685>
327. Mariappan, P., *et al.* Stone and pelvic urine culture and sensitivity are better than bladder urine as predictors of urosepsis following percutaneous nephrolithotomy: a prospective clinical study. *J Urol*, 2005. 173: 1610.
<https://www.ncbi.nlm.nih.gov/pubmed/15821509>
328. Osman, M., *et al.* Percutaneous nephrolithotomy with ultrasonography-guided renal access: experience from over 300 cases. *BJU Int*, 2005. 96: 875.
<https://www.ncbi.nlm.nih.gov/pubmed/16153221>
329. Rao, P.N., *et al.* Prediction of septicemia following endourological manipulation for stones in the upper urinary tract. *J Urol*, 1991. 146: 955.
<https://www.ncbi.nlm.nih.gov/pubmed/1895450>
330. Seyrek, M., *et al.* Perioperative prophylaxis for percutaneous nephrolithotomy: randomized study concerning the drug and dosage. *J Endourol*, 2012. 26: 1431.
<https://www.ncbi.nlm.nih.gov/pubmed/22612061>
331. Bierkens, A.F., *et al.* The value of antibiotic prophylaxis during extracorporeal shock wave lithotripsy in the prevention of urinary tract infections in patients with urine proven sterile prior to treatment. *Eur Urol*, 1997. 31: 30.
<https://www.ncbi.nlm.nih.gov/pubmed/9032531>
332. Charton, M., *et al.* Use of antibiotics in the conjunction with extracorporeal lithotripsy. *Eur Urol*, 1990. 17: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/2178940>
333. Claes, H., *et al.* Amoxicillin/clavulanate prophylaxis for extracorporeal shock wave lithotripsy - a comparative study. *J Antimicrob Chemother*, 1989. 24 Suppl B: 217.
<https://www.ncbi.nlm.nih.gov/pubmed/2691484>
334. Deliveliotis, C., *et al.* The necessity of prophylactic antibiotics during extracorporeal shock wave lithotripsy. *Int Urol Nephrol*, 1997. 29: 517.
<https://www.ncbi.nlm.nih.gov/pubmed/9413755>
335. Dincel, C., *et al.* Incidence of urinary tract infection in patients without bacteriuria undergoing SWL: comparison of stone types. *J Endourol*, 1998. 12: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/9531141>

336. Gattegno, B., *et al.* [Extracorporeal lithotripsy and prophylactic antibiotic therapy]. *Ann Urol (Paris)*, 1988. 22: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/3382159>
337. Knipper, A., *et al.* [Antibiotic prophylaxis with enoxacin in extracorporeal shockwave lithotripsy]. *Infection*, 1989. 17 Suppl 1: S37.
<https://www.ncbi.nlm.nih.gov/pubmed/2807562>
338. Lu, Y., *et al.* Antibiotic prophylaxis for shock wave lithotripsy in patients with sterile urine before treatment may be unnecessary: a systematic review and meta-analysis. *J Urol*, 2012. 188: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/22704118>
339. Pearle, M.S., *et al.* Antimicrobial prophylaxis prior to shock wave lithotripsy in patients with sterile urine before treatment: a meta-analysis and cost-effectiveness analysis. *Urology*, 1997. 49: 679.
<https://www.ncbi.nlm.nih.gov/pubmed/9145970>
340. Pettersson, B., *et al.* Are prophylactic antibiotics necessary during extracorporeal shockwave lithotripsy? *Br J Urol*, 1989. 63: 449.
<https://www.ncbi.nlm.nih.gov/pubmed/2659132>
341. Kiddoo, D.A., *et al.* A population based assessment of complications following outpatient hydrocelectomy and spermatocelectomy. *J Urol*, 2004. 171: 746.
<https://www.ncbi.nlm.nih.gov/pubmed/14713801>
342. Montgomery, J.S., *et al.* Wound complications after hand assisted laparoscopic surgery. *J Urol*, 2005. 174: 2226.
<https://www.ncbi.nlm.nih.gov/pubmed/16280775>
343. Pessaux, P., *et al.* Risk factors for prediction of surgical site infections in "clean surgery". *Am J Infect Control*, 2005. 33: 292.
<https://www.ncbi.nlm.nih.gov/pubmed/15947746>
344. Steiner, T., *et al.* [Perioperative antibiotic prophylaxis in transperitoneal tumor nephrectomy: does it lower the rate of clinically significant postoperative infections?]. *Urologe A*, 2003. 42: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/12574881>
345. Swartz, M.A., *et al.* Complications of scrotal surgery for benign conditions. *Urology*, 2007. 69: 616.
<https://www.ncbi.nlm.nih.gov/pubmed/17445635>
346. Richter, S., *et al.* Infected urine as a risk factor for postprostatectomy wound infection. *Infect Control Hosp Epidemiol*, 1991. 12: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/2022859>
347. Hara, N., *et al.* Perioperative antibiotics in radical cystectomy with ileal conduit urinary diversion: efficacy and risk of antimicrobial prophylaxis on the operation day alone. *Int J Urol*, 2008. 15: 511.
<https://www.ncbi.nlm.nih.gov/pubmed/18422576>
348. Mangram, A.J., *et al.* Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control*, 1999. 27: 97.
<https://www.ncbi.nlm.nih.gov/pubmed/10196487>
349. Studer, U.E., *et al.* Experience in 100 patients with an ileal low pressure bladder substitute combined with an afferent tubular isoperistaltic segment. *J Urol*, 1995. 154: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/7776455>
350. Takeyama, K., *et al.* Incidence of and risk factors for surgical site infection in patients with radical cystectomy with urinary diversion. *J Infect Chemother*, 2005. 11: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/16133708>
351. Carson, C.C. Diagnosis, treatment and prevention of penile prosthesis infection. *Int J Impot Res*, 2003. 15 Suppl 5: S139.
<https://www.ncbi.nlm.nih.gov/pubmed/14551594>
352. Kabalin, J.N., *et al.* Infectious complications of penile prosthesis surgery. *J Urol*, 1988. 139: 953.
<https://www.ncbi.nlm.nih.gov/pubmed/3361672>
353. Mould, J.W., *et al.*, Infectious complications of penile prostheses, in *Infections in Urology* 1989.
354. Radomski, S.B., *et al.* Risk factors associated with penile prosthesis infection. *J Urol*, 1992. 147: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/1732599>
355. Health and Social Care Information Centre: Hospital Episode Statistics Admitted Patient Care, England 2013-14. 2015.
<http://content.digital.nhs.uk/catalogue/PUB16719/hosp-epis-stat-admi-summ-rep-2013-14-rep.pdf>
356. Brewster, S., *et al.* 5A prospective survey of current prostate biopsy practices among oncological urologists. *Can J Urol*, 2010. 17: 5071.
<https://www.ncbi.nlm.nih.gov/pubmed/20398444>

357. Wagenlehner, F.M., *et al.* Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. *Eur Urol*, 2013. 63: 521.
<https://www.ncbi.nlm.nih.gov/pubmed/22704727>
358. Bruyere, F., *et al.* Is urine culture routinely necessary before prostate biopsy? *Prostate Cancer and Prostatic Diseases*, 2010. 13: 260.
<https://www.ncbi.nlm.nih.gov/pubmed/20368725>
359. Emiliozzi, P., *et al.* The incidence of prostate cancer in men with prostate specific antigen greater than 4.0 ng/ml: a randomized study of 6 versus 12 core transperineal prostate biopsy. *J Urol*, 2004. 171: 197.
<https://www.ncbi.nlm.nih.gov/pubmed/14665875>
360. Irani, J., *et al.* Is an extended 20-core prostate biopsy protocol more efficient than the standard 12-core? A randomized multicenter trial. *J Urol*, 2013. 190, 77.
<https://www.ncbi.nlm.nih.gov/pubmed/23313205>
361. Mariappan, P., *et al.* Increasing prostate biopsy cores based on volume vs the sextant biopsy: A prospective randomized controlled clinical study on cancer detection rates and morbidity. *BJU Int*, 2004. 94: 307.
<https://www.ncbi.nlm.nih.gov/pubmed/15291857>
362. Naughton, C.K., *et al.* Pain and morbidity of transrectal ultrasound guided prostate biopsy: a prospective randomized trial of 6 versus 12 cores. *J Urol*, 2000. 163, 168.
<https://www.ncbi.nlm.nih.gov/pubmed/10604338>
363. Paul, R., *et al.* Morbidity of prostatic biopsy for different biopsy strategies: Is there a relation to core number and sampling region? *European Urology*, 2004. 45: 450.
<https://www.ncbi.nlm.nih.gov/pubmed/15041108>
364. Rodríguez-Covarrubias, F., *et al.* Extended sampling at first biopsy improves cancer detection rate: results of a prospective, randomized trial comparing 12 versus 18-core prostate biopsy. *J Urol*, 2011. 185, 2132.
<https://www.ncbi.nlm.nih.gov/pubmed/21496851>
365. Sur, R.L., *et al.* A prospective randomized comparison of extensive prostate biopsy to standard biopsy with assessment of diagnostic yield, biopsy pain and morbidity. *Prostate Cancer and Prostatic Diseases*, 2004. 7: 126.
<https://www.ncbi.nlm.nih.gov/pubmed/15111980>
366. Adamakis, I., *et al.* Pain during transrectal ultrasonography guided prostate biopsy: a randomized prospective trial comparing periprostatic infiltration with lidocaine with the intrarectal instillation of lidocaine-prilocain cream. *World J Urol*, 2004. 22: 281.
<https://www.ncbi.nlm.nih.gov/pubmed/14689224>
367. Aktoz, T., *et al.* 'Multimodal' approach to management of prostate biopsy pain and effects on sexual function: Efficacy of levobupivacaine adjuvant to diclofenac sodium - A prospective randomized trial. *Andrologia*, 2010. 42: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/20078514>
368. Alavi, A.S., *et al.* Local anesthesia for ultrasound guided prostate biopsy: a prospective randomized trial comparing 2 methods. *J Urol*, 2001. 166, 1343.
<http://www.sciencedirect.com/science/article/pii/S0022534705657655>
369. Basar, M.M., *et al.* Local anesthesia in transrectal ultrasound-guided prostate biopsy: EMLA cream as a new alternative technique. *Scandinavian J Urol Nephrol*, 2005. 39: 130.
<https://www.ncbi.nlm.nih.gov/pubmed/16019766>
370. Cormio, L., *et al.* Combined perianal-intrarectal (PI) lidocaine-prilocaine (LP) cream and lidocaine-ketorolac gel provide better pain relief than combined PI LP cream and periprostatic nerve block during transrectal prostate biopsy. *BJU Int*, 2012. 109, 1776.
<https://www.ncbi.nlm.nih.gov/pubmed/21999406>
371. D'Eramo, G., *et al.* Comparison between ultrasound-guided and digital-guided anesthesia before prostatic biopsy. *Archivio Italiano di Urologia e Andrologia*, 2012. 84: 260.
<https://www.ncbi.nlm.nih.gov/pubmed/23427759>
372. Giannarini, G., *et al.* Combination of Perianal-Intrarectal Lidocaine-Prilocaine Cream and Periprostatic Nerve Block for Pain Control During Transrectal Ultrasound Guided Prostate Biopsy: A Randomized, Controlled Trial. *J Urol*, 2009. 181: 585.
<https://www.ncbi.nlm.nih.gov/pubmed/19084860>

373. Gurbuz, C., *et al.* Visual pain score during transrectal ultrasound-guided prostate biopsy using no anaesthesia or three different types of local anaesthetic application. *Scan J Urol Nephrol*, 2010. 44: 212.
<https://www.ncbi.nlm.nih.gov/pubmed/20377490>
374. Hiros, M., *et al.* Transrectal ultrasound-guided prostate biopsy, periprostatic local anesthesia and pain tolerance. *Bosn J Basic Med Sci*, 2010. 10: 68.
<https://www.ncbi.nlm.nih.gov/pubmed/20192935>
375. Kim, S., *et al.* Effect of oral administration of acetaminophen and topical application of emla on pain during transrectal ultrasound-guided prostate biopsy. *Korean J Urol*, 2011. 52: 452.
<https://www.ncbi.nlm.nih.gov/pubmed/21860764>
376. Klein, T., *et al.* The impact of prostate biopsy and periprostatic nerve block on erectile and voiding function: a prospective study. *J Urol*, 2010. 184, 1447.
<https://www.ncbi.nlm.nih.gov/pubmed/20727540>
377. Liu, B.Q., *et al.* [Comparison of three different methods of anesthesia during transrectal ultrasound guided prostate biopsy: a prospective, double-blind, randomized trial.]. *Zhonghua Wai Ke Za Zhi*, 2009. 47: 1651.
<https://www.ncbi.nlm.nih.gov/pubmed/20137402>
378. Mallick, S., *et al.* Which anaesthesia should be recommended for prostate biopsy? *West Indian Med J*, 2005. 54: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/15999885>
379. Obek, C., *et al.* Is periprostatic local anesthesia for transrectal ultrasound guided prostate biopsy associated with increased infectious or hemorrhagic complications? A prospective randomized trial. *J Urol*, 2002. 168: 558.
<https://www.ncbi.nlm.nih.gov/pubmed/12131309>
380. Park, S.M., *et al.* The effects of combination of intrarectal lidocaine-gel with periprostatic lidocaine injection on the pain relief in repeated transrectal prostate biopsy. [Korean]. *Korean J Urol*, 2005. 46, 1051.
<https://www.researchgate.net/publication/287475198>
381. Ragavan, N., *et al.* A randomized, controlled trial comparing lidocaine periprostatic nerve block, diclofenac suppository and both for transrectal ultrasound guided biopsy of prostate. *J Urol*, 2005. 174: 510.
<https://www.ncbi.nlm.nih.gov/pubmed/16006882>
382. Sataa, S., *et al.* [Local anesthesia in transrectal ultrasound-guided prostate biopsy: apical periprostatic nerve block versus endorectal lidocaine gel. A randomized controlled trial of 100 patients]. *La Tunisie médicale*, 2010. 88, 217.
<https://www.ncbi.nlm.nih.gov/pubmed/20446252>
383. Seymour, H., *et al.* Pain after transrectal ultrasonography-guided prostate biopsy: the advantages of periprostatic local anaesthesia. *BJU Int*, 2001. 88: 540.
<https://www.ncbi.nlm.nih.gov/pubmed/11678747>
384. Song, S.H., *et al.* Effectiveness of local anaesthesia techniques in patients undergoing transrectal ultrasound-guided prostate biopsy: A prospective randomized study. *International J Urol*, 2006. 13: 707.
<https://www.ncbi.nlm.nih.gov/pubmed/16834647>
385. Szlauer, R., *et al.* Comparison of lidocaine suppositories and periprostatic nerve block during transrectal prostate biopsy. *Urol Int*, 2008. 80: 253.
<https://www.ncbi.nlm.nih.gov/pubmed/18480626>
386. Trucchi, A., *et al.* Local anesthesia reduces pain associated with transrectal prostatic biopsy. A prospective randomized study. *Urol Int*, 2005. 74, 209.
<https://www.ncbi.nlm.nih.gov/pubmed/15812205>
387. Xiangkui, L., *et al.* Lidocaine Hydrochloride Injection preventing pain in patients who underwent transrectal ultrasound-guided prostate biopsy: A single center, prospective, randomized single-blind, placebo-controlled clinical trial. *Chin J Androl*, 2009. 23: 25. [No abstract available].
388. Xu, N., *et al.* Meperidine relieves pain during transrectal ultrasound-guided prostate biopsy. *Saudi Med J*, 2014. 35: 454.
<https://www.ncbi.nlm.nih.gov/pubmed/24825805>
389. Chae, Y., *et al.* The Comparison between Transperineal and Transrectal Ultrasound-Guided Prostate Needle Biopsy. *Korean J Urol*, 2009. 50: 119.
<https://synapse.koreamed.org/search.php?where=aview&id=10.4111/kju.2009.50.2.119&code=0020KJU&vmode=FULL>

390. Hara, R., *et al.* Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. *Urology*, 2008. 71: 191.
<https://www.ncbi.nlm.nih.gov/pubmed/18308081>
391. Takenaka, A., *et al.* A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. *Prostate Cancer Prostatic Dis*, 2008. 11: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/17533394>
392. Abughosh, Z., *et al.* A prospective randomized trial of povidone-iodine prophylactic cleansing of the rectum before transrectal ultrasound guided prostate biopsy. *J Urol*, 2013. 189.
<https://www.ncbi.nlm.nih.gov/pubmed/23041343>
393. Brown, R.W., *et al.* Bacteremia and bacteriuria after transrectal prostatic biopsy. *Urology*, 1981. 18, 145.
<https://www.ncbi.nlm.nih.gov/pubmed/7269016>
394. Ghafoori, M., *et al.* Decrease in infection rate following use of povidone-iodine during transrectal ultrasound guided biopsy of the prostate: a double blind randomized clinical trial. *Iranian J Radiol*, 2012. 9: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/23329966>
395. Kanjanawongdeengam, P., *et al.* Reduction in bacteremia rates after rectum sterilization before transrectal, ultrasound-guided prostate biopsy: a randomized controlled trial. *Chotmaihet thangphaet [J Med Assoc Thai]* 2009. 92, 1621.
<https://www.ncbi.nlm.nih.gov/pubmed/20043564>
396. Sharpe, J.R., *et al.* Urinary tract infection after transrectal needle biopsy of the prostate. *J Urol*, 1982. 127: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/7062377>
397. Melekos, M.D. Efficacy of prophylactic antimicrobial regimens in preventing infectious complications after transrectal biopsy of the prostate. *International Urology Nephrol*, 1990. 22: 257.
<https://www.ncbi.nlm.nih.gov/pubmed/2210982>
398. Taher, Y., *et al.* Prospective randomized controlled study to assess the effect of perineal region cleansing with povidone iodine before transrectal needle biopsy of the prostate on infectious complications. *Urology*, 2014. 84, S306.
[http://www.jurology.com/article/S0022-5347\(15\)01996-5/abstract](http://www.jurology.com/article/S0022-5347(15)01996-5/abstract)
399. Herrera-Caceres, J.O., *et al.* Utility of enemas before transrectal prostate biopsies: Preliminary report. *J Urol*, 2015. Conference: 2015 Annual Meeting of the American Urological Association.
<https://www.ncbi.nlm.nih.gov/pubmed/71858463>
400. Lindert, K.A., *et al.* Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. *J Urol*, 2000. 164: 76.
<https://www.ncbi.nlm.nih.gov/pubmed/10840428>
401. Caskurlu, T., *et al.* Prevalence of antibiotic resistance in fecal flora before transrectal ultrasound-guided prostate biopsy and clinical impact of targeted antibiotic prophylaxis. *J Urol*, 2015. Conference: 2015 Annual Meeting of the American Urological Association.
<https://www.ncbi.nlm.nih.gov/pubmed/71859172>
402. Gurbuz, C., *et al.* Reducing infectious complications after transrectal prostate needle biopsy using a disposable needle guide: is it possible? *Int Braz J Urol*. 2011. 37: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/21385483>
403. Tuncel, A., *et al.* Does disposable needle guide minimize infectious complications after transrectal prostate needle biopsy? *Urology*, 2008. 71, 1024.
<https://www.ncbi.nlm.nih.gov/pubmed/18400273>
404. Koc, G., *et al.* Does washing the biopsy needle with povidone-iodine have an effect on infection rates after transrectal prostate needle biopsy? *Urologia Internationalis*, 2010. 85: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/20453481>
405. Akan, H., *et al.* Comparison of two periprostatic nerve blockade techniques for transrectal ultrasound-guided prostate biopsy: bilateral basal injection and single apical injection. *Urology*, 2009. 73, 23.
<https://www.ncbi.nlm.nih.gov/pubmed/18829075>
406. Ould Ismail, T., *et al.* The contribution of periapical nerve block in transrectal ultrasound-guided prostate biopsy: Results from a prospective randomized trial. *African J Urol*, 2012. 18, 78.
<http://www.sciencedirect.com/science/article/pii/S1110570412000173>

407. Cevik, I., *et al.* Combined “periprostatic and periapical” local anesthesia is not superior to “periprostatic” anesthesia alone in reducing pain during Tru-Cut prostate biopsy. *Urology*, 2006. 68, 1215.
<https://www.ncbi.nlm.nih.gov/pubmed/17169645>
408. Cantiello, F., *et al.* Pelvic plexus block is more effective than periprostatic nerve block for pain control during office transrectal ultrasound guided prostate biopsy: A single center, prospective, randomized, double arm study. *J Urol*, 2012. 188: 417.
<https://www.ncbi.nlm.nih.gov/pubmed/22704121>
409. Toi, A., *et al.* Does the addition of apical injection of local anesthesia to basal injection diminish pain related to transrectal ultrasound guided prostate biopsy? *J Urol*, 2012. Conference: 2012 Annual Meeting of the American Urological Association.
[http://www.jurology.com/article/S0022-5347\(12\)02756-5/abstract](http://www.jurology.com/article/S0022-5347(12)02756-5/abstract)
410. Agbugui, J.O., *et al.* Antibiotic prophylaxis for transrectal prostate biopsy: a comparison of one-day and five-day regimen. *Niger Postgrad Med J*, 2014. 21: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/25331236>
411. Akay, A.F., *et al.* Prevention of pain and infective complications after transrectal prostate biopsy: a prospective study. *Int Urol Nephrol*, 2006. 38, 45.
<https://www.ncbi.nlm.nih.gov/pubmed/16502051>
412. Argyropoulos, A.N., *et al.* Time of administration of a single dose of oral levofloxacin and its effect in infectious complications from transrectal prostate biopsy. *Int Urol Nephrol*, 2007. 39: 897.
<https://www.ncbi.nlm.nih.gov/pubmed/17203352>
413. Aron, M., *et al.* Antibiotic prophylaxis for transrectal needle biopsy of the prostate: A randomized controlled study. *BJU Int*, 2000. 85: 682.
<https://www.ncbi.nlm.nih.gov/pubmed/10759665>
414. Aus, G., *et al.* Infection after transrectal core biopsies of the prostate--risk factors and antibiotic prophylaxis. *Brit J Urol* 77, 1996. 851.
<https://www.ncbi.nlm.nih.gov/pubmed/8705220>
415. Bates, T.S., *et al.* Prophylaxis for transrectal prostatic biopsies: A randomized controlled study of intravenous co-amoxiclav given as a single dose compared with an intravenous dose followed by oral co-amoxiclav for 24 h. *Brit J Urol*, 1998. 81: 529.
<https://www.ncbi.nlm.nih.gov/pubmed/9598622>
416. Bosquet Sanz, M., *et al.* Comparative study between tobramycin and tobramycin plus ciprofloxacin in transrectal prostate biopsy prophylaxis. *Actas urologicas espanolas*, 2006. 30: 866.
<https://www.ncbi.nlm.nih.gov/pubmed/17175926>
417. Brewster, S.F., *et al.* Antimicrobial prophylaxis for transrectal prostatic biopsy: A prospective randomized trial of cefuroxime versus piperacillin/tazobactam. *Brit J Urol*, 1995. 76: 351.
<https://www.ncbi.nlm.nih.gov/pubmed/7551845>
418. Briffaux, R., *et al.* One preoperative dose randomized against 3-day antibiotic prophylaxis for transrectal ultrasonography-guided prostate biopsy. *BJU Int*, 2009. 103, 106.
<https://www.ncbi.nlm.nih.gov/pubmed/>
419. Cam, K., *et al.* Prospective assessment of the efficacy of single dose versus traditional 3-day antimicrobial prophylaxis in 12-core transrectal prostate biopsy. *International J Urol*, 1001. 15: 997.
<https://www.ncbi.nlm.nih.gov/pubmed/18721198>
420. Chan, E.S., *et al.* Randomized controlled trial of antibiotic prophylaxis regimens for transrectal ultrasound-guided prostate biopsy. *Chin Med J*, 2012. 125, 2432.
<https://www.ncbi.nlm.nih.gov/pubmed/22882916>
421. Chazan, B., *et al.* Antimicrobial prophylaxis for transrectal ultrasound guided biopsy of prostate: A comparative study between single dose of Gentamicin vs. Ofloxacin. *Int J Infect Dis*, 2010. Conference: 14th International Congress on Infectious Diseases (ICID) Miami.
<https://www.ncbi.nlm.nih.gov/pubmed/70125506>
422. Cormio, L., *et al.* Antimicrobial prophylaxis for transrectal prostatic biopsy: A prospective study of ciprofloxacin vs piperacillin/tazobactam. *BJU Int*, 2002. 90: 700.
<https://www.ncbi.nlm.nih.gov/pubmed/12410751>
423. Crawford, E.D., *et al.* Prevention of urinary tract infection and sepsis following transrectal prostatic biopsy. *J Urol*, 1982. 127, 449.
<https://www.ncbi.nlm.nih.gov/pubmed/6895918>
424. Ergakov, D.V., *et al.* [Efficiency of safocid in the prevention of infectious and inflammatory complications after prostate biopsy]. *Urologii[combining double inverted breve]a*, 1999. 6: 48.
<https://www.ncbi.nlm.nih.gov/pubmed/24649764>

425. Ferreira, U., *et al.* A comparative study of the local and systemic use of sulfamethoxazole-trimethoprim in the transrectal biopsy of the prostate. *Archivos Espanoles de Urologia*, 1985. 38: 301.
<https://www.ncbi.nlm.nih.gov/pubmed/3933438>
426. Fong, I.W., *et al.* A randomized comparative study of the prophylactic use of trimethoprim-sulfamethoxazole versus netilmycin-metronidazole in transrectal prostatic biopsy. *J Urol*, 1991. 146: 794.
<https://www.ncbi.nlm.nih.gov/pubmed/1908529>
427. Heidari Bateni, Z., *et al.* Single-dose versus multiple-dose ciprofloxacin plus metronidazole prophylaxis in transrectal ultrasound-guided biopsy of the prostate: a randomized controlled trial. *Acta Medica Iranica*, 2014. 52: 664.
<https://www.ncbi.nlm.nih.gov/pubmed/25325203>
428. Herranz Amo, F., *et al.* Morbidity of and tolerance to ultrasonography-guided transrectal biopsy of the prostate. *Actas urologicas espanolas*, 1996. 20: 858.
<https://www.ncbi.nlm.nih.gov/pubmed/9139527>
429. Inal, G., *et al.* Periprostatic nerve blockade before transrectal ultrasound-guided prostate biopsy: the Ankara Numune experience. *Urol Int*, 2003. 71: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/12890954>
430. Inal, G., *et al.* Comparison of 2 ml and 6 ml of periprostatic 1% lidocaine injections before transrectal ultrasound guided prostate biopsy. *Turk Uroloji Dergisi*, 2004. 30: 173. [No abstract available].
431. Isen, K., *et al.* Antibiotic prophylaxis for transrectal biopsy of the prostate: A prospective randomized study of the prophylactic use of single dose oral fluoroquinolone versus trimethoprim-sulfamethoxazole. *Int Urol Nephrol*, 1999. 31: 491.
<https://www.ncbi.nlm.nih.gov/pubmed/10668944>
432. Ito, Y., *et al.* Antimicrobial prophylaxis for transrectal prostatic biopsy: A prospective randomized trial using levofloxacin. *J Chemother*, 2002. 50: 870. [No abstract available].
433. Kapoor, D.A., *et al.* Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. *Urology*, 1998. 52: 552.
<https://www.ncbi.nlm.nih.gov/pubmed/9763070>
434. Knobloch, R., *et al.* Bilateral fine-needle administered local anaesthetic nerve block for pain control during TRUS-guided multi-core prostate biopsy: a prospective randomised trial. *Eur Urol*, 2002. 41, 508.
<https://www.ncbi.nlm.nih.gov/pubmed/12074792>
435. Lista, F., *et al.* Efficacy and safety of fosfomycin-trometamol in the prophylaxis for transrectal prostate biopsy. Prospective randomized comparison with ciprofloxacin. *Actas Urologicas Espanolas*, 2014. 38: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/24775812>
436. Mari, M. Single dose versus 5-day course of oral prulifloxacin in antimicrobial prophylaxis for transrectal prostate biopsy. *Minerva Urol Nefrol*, 2007. 59: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/17431366>
437. Meyer, W.H., *et al.* Transrectal prostatic biopsy: The incidence of fever and sepsis after treatment with antibiotics. *Aktuelle Urologie*, 1987. 18: 22. [No abstract available].
438. Pace, G., *et al.* Cephalosporins periprostatic injection: Are really effective on infections following prostate biopsy? *Int Urol Nephrol*, 2012. 44, 1065.
<https://www.ncbi.nlm.nih.gov/pubmed/22434340>
439. Palmieri, F., *et al.* Single-dose versus 5-day antibiotic therapy in patients undergoing transrectal prostate biopsy: Our preliminary experience. *Anticancer Research*, 2010. Conference: 20th Annual Meeting of the Italian Society of Uro.
<https://www.ncbi.nlm.nih.gov/pubmed/70219544>
440. Peters, H.J., *et al.* Antibiotic prophylaxis in transrectal prostate biopsies: Short- and long-term treatment. *Urologe Ausgabe A*, 2003. 42: 91.
<https://www.researchgate.net/publication/8975569>
441. Petteffi, L., *et al.* Efficiency of short and long term antimicrobial therapy in transrectal ultrasound-guided prostate biopsies. *Int Braz J Urol*, 2002. 28: 526.
<https://www.ncbi.nlm.nih.gov/pubmed/15748401>
442. Ruebush, I.T.K., *et al.* A double-blind study of trimethoprim-sulfamethoxazole prophylaxis in patients having transrectal needle biopsy of the prostate. *J Urol*, 1979. 122: 492.
<https://www.ncbi.nlm.nih.gov/pubmed/384025>

443. Sabbagh, R., *et al.* A prospective randomized trial of 1-day versus 3-day antibiotic prophylaxis for transrectal ultrasound guided prostate biopsy. *Can J Urol*, 2004. 11, 2216.
<https://www.ncbi.nlm.nih.gov/pubmed/15182413>
444. Schaeffer, A.J., *et al.* Comparison of a 3-day with a 1-day regimen of an extended-release formulation of ciprofloxacin as antimicrobial prophylaxis for patients undergoing transrectal needle biopsy of the prostate. *BJU Int*, 2007. 100: 51.
<https://www.ncbi.nlm.nih.gov/pubmed/17552953>
445. Shivde, S.R., *et al.* Trimethoprim versus gentamicin for the prevention of bacteriuria following transrectal biopsy of the prostate - Do patients need additional anaerobic cover? *Urologia Internationalis*, 2002. 69: 106.
<https://www.ncbi.nlm.nih.gov/pubmed/12187039>
446. Tas, M., *et al.* Comparison of patient comfort and complications of transrectal ultrasonography guided prostate biopsies using 16 and 18 Gauge needles. *Turk Uroloji Dergisi*, 2005. 31: 119.
<http://www.turkurolojidergisi.com/eng/ozet/1097/32/Abstract>
447. Tekdogan, U., *et al.* The efficiency of prophylactic antibiotic treatment in patients without risk factor who underwent transrectal. *Turk Uroloji Dergisi*, 2006. 32: 261.
<https://www.researchgate.net/publication/289651865>
448. Thompson, P.M., *et al.* The problem of infection after prostatic biopsy: The case for the transperineal approach. *Brit J Urol*, 1982. 54: 736.
<https://www.ncbi.nlm.nih.gov/pubmed/7150932>
449. Vaz, F., *et al.* The use of lomefloxacin in the prophylaxis of transrectal prostate biopsy. *Revis Brasil Med*, 1994. 51: 1709. [No abstract available].
450. Wang, H., *et al.* Investigation of infection risk and the value of antibiotic prophylaxis during transrectal biopsy of the prostate by endotoxin determination. *Zhonghua nan ke xue =, Nat J Androl*, 2004. 10: 496.
<https://www.ncbi.nlm.nih.gov/pubmed/15354517>
451. Yamamoto, S., *et al.* Antibiotic prophylaxis for transrectal prostate biopsy: A prospective randomized study of tosufloxacin versus levofloxacin. *Int J Urol*, 2008. 15: 604.
<https://www.ncbi.nlm.nih.gov/pubmed/18462354>
452. Yang, L., *et al.* Clinical significance of antibiotic prophylaxis for transrectal prostate biopsy. *Zhonghua wai ke za zhi [Chin J Surg]*, 2001. 39: 940.
<https://www.ncbi.nlm.nih.gov/pubmed/16201177>
453. Yu, L., *et al.* Impact of insertion timing of iodophor cotton ball on the control of infection complications after transrectal ultrasound guided prostate biopsy. *Nat Med J China*, 2014. 94: 609.
<https://www.ncbi.nlm.nih.gov/pubmed/24762693>
454. Zani, E.L., *et al.* Antibiotic prophylaxis for transrectal prostate biopsy. *Cochrane database of systematic reviews*, 2011. 5.
<https://www.ncbi.nlm.nih.gov/pubmed/21563156>
455. Walker, J.T., *et al.* Reducing Infectious Complications Following Transrectal Ultrasound-guided Prostate Biopsy: A Systematic Review. *Rev Urol*, 2016. 18: 73.
<https://www.ncbi.nlm.nih.gov/pubmed/27601966>

5. CONFLICT OF INTEREST

All members of the EAU Urological Infections Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: <http://www.uroweb.org/guidelines/>. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.



EAU Guidelines on Urolithiasis

C. Türk (Chair), A. Neisius, A. Petrik, C. Seitz,
A. Skolarikos, A. Tepeler, K. Thomas
Guidelines Associates: S. Dabestani, T. Drake,
N. Grivas, Y. Ruhayel

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urolithiasis Guidelines Panel has prepared these guidelines to help urologists assess evidence-based management of stones/calculi in the urinary tract and incorporate recommendations into clinical practice. Management of bladder stones is not addressed in these guidelines. This document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Panel is aware of the geographical variations in healthcare provision.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account.

Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urolithiasis Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: <http://uroweb.org/guideline/urolithiasis/>.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text versions. Also a number of scientific publications are available [1-3]. All documents can be accessed through the EAU website: <http://uroweb.org/guideline/urolithiasis/>.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU Urolithiasis Guidelines were first published in 2000. This 2017 document presents a limited update of the 2016 publication of the EAU Urolithiasis Guidelines.

1.4.2 Summary of changes

The literature for the entire document has been assessed and updated, whenever relevant (see Methods section below).

Key changes for the 2017 publication:

3.4.1.1 Renal colic

Summary of evidence	LE
Administration of daily α -blockers seems to reduce colic episodes, although controversy remains in the published literature.	1b

3.4.2.1.3.2 Best clinical practice

Summary of evidence - Number of shock waves, energy setting and repeat treatment sessions	LE
Stepwise power ramping prevents renal injury.	1b
Clinical experience has shown that repeat sessions are feasible (within one day for ureteral stones).	4
Optimal shock wave frequency is 1.0 to 1.5Hz.	1a

3.4.2.2 Indication for active stone removal of renal stones

Recommendation	GR
Offer active treatment for renal stones in case of stone growth, <i>de novo</i> obstruction, associated infection, and acute and/or chronic pain.	C

3.4.3.1.2 Pharmacological treatment, Medical expulsive therapy (MET)

Summary of evidence	LE
Medical expulsion therapy (MET) seems to be efficacious treating patients with ureteric stones who are amenable to conservative management. The greatest benefit might be among those with larger (distal) stones.	1a

Recommendations	LE	GR
Select patients for an attempt at spontaneous passage or MET, based on well-controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve.	4	C
Offer α -blockers as MET as one of the treatment options, in particular for (distal) ureteral stones > 5 mm.	1a	A
Counsel patients regarding the controversies in the literature, attendant risks of MET, including associated drug side effects. Inform the patient that α -blockers as MET are administered off-label ^{†**} .	1b	A*

[†] It is not known if tamsulosin harms the human foetus or if it is found in breast milk.

*Upgraded based on panel consensus.

**MET in children cannot be recommended due to the limited data in this specific population.

3.4.3.1.4.1.2 Best clinical practice in ureteroscopy

Summary of evidence	LE
In ureteroscopy (URS) (in particular for renal stones), pre-stenting has been shown to improve outcome.	1b

3.4.3.3 Selection of procedure for active removal of ureteral stones

Recommendation	GR
In obese patients ureteroscopy is a safe and efficient option to remove renal stones.	2b
Ureteroscopy in morbidly obese patients have significantly higher complication rates as compared to normal weight patients.	1a

2. METHODS

2.1 Data identification

For the 2017 Urolithiasis Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the guideline was performed. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published between September 1st 2015 and October 12th, 2016. Databases covered by the search included Medline, EMBASE and the Cochrane Libraries. A total of 751 unique records were identified, and screened for relevance. The search strategy is published online: <http://uroweb.org/guideline/urolithiasis/?type=appendices-publications>.

In addition to the new literature identified through the electronic searches, the authors included one additional, more recent, article as of significant relevance for two sections (3.4.1.1 Renal colic & 3.4.3.1.2 Pharmacological treatment, Medical expulsive therapy (MET) [4].

Two sections of the text have been updated based on two systematic reviews (SRs). These SRs were performed using standard Cochrane SR methodology; <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>.

Systematic review topics:

- Tract sizes in miniaturized percutaneous nephrolithotomy: A systematic review [5].
- What are the benefits and harms of ureteroscopy (URS) compared with shock-wave lithotripsy (SWL) in the treatment of upper ureteral stones (UUS): A systematic review [6].
-

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>.

A list of Associations endorsing the EAU Guidelines can also be viewed on line at the above address.

2.2 Review

The 2015 Urolithiasis Guidelines were subjected to peer review prior to publication.

2.3 Future goals

Further results on ongoing and new SRs will be included in the 2018 update of the Urolithiasis Guidelines.

3. GUIDELINES

3.1 Prevalence, aetiology, risk of recurrence

3.1.1 Introduction

Stone incidence depends on geographical, climatic, ethnic, dietary and genetic factors. The recurrence risk is basically determined by the disease or disorder causing the stone formation. Accordingly, the prevalence rates for urinary stones vary from 1% to 20% [8]. In countries with a high standard of life such as Sweden, Canada or the US, renal stone prevalence is notably high (> 10%). For some areas an increase of more than 37% over the last 20 years has been reported [9-11].

Stones can be classified into those caused by: infection, or non-infectious causes (infection- and non-infection stones); genetic defects [12]; or adverse drug effects (drug stones) (Table 3.1.1).

Table 3.1.1: Stones classified by aetiology*

Non-infection stones
Calcium oxalate
Calcium phosphate
Uric acid
Infection stones
Magnesium ammonium phosphate
Carbonate apatite
Ammonium urate
Genetic causes
Cystine
Xanthine
2,8-Dihydroxyadenine
Drug stones

*See Section 4.4.2

3.1.2 Stone composition

Stone composition is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of substances. Table 3.1.2 lists the clinically most relevant substances and their mineral components.

Table 3.1.2: Stone composition

Chemical name	Mineral name	Chemical formula
Calcium oxalate monohydrate	Whewellite	CaC ₂ O ₄ .H ₂ O
Calcium oxalate dihydrate	Wheddelite	CaC ₂ O ₄ .2H ₂ O
Basic calcium phosphate	Apatite	Ca ₁₀ (PO ₄) ₆ .(OH) ₂
Calcium hydroxyl phosphate	Carbonite apatite	Ca ₅ (PO ₃) ₃ (OH)
b-tricalcium phosphate	Whitlockite	Ca ₃ (PO ₄) ₂
Carbonate apatite phosphate	Dahllite	Ca ₅ (PO ₄) ₃ OH
Calcium hydrogen phosphate	Brushite	PO ₄ .2H ₂ O
Calcium carbonate	Aragonite	CaCO ₃
Octacalcium phosphate		Ca ₈ H ₂ (PO ₄) ₆ .5H ₂ O
Uric acid	Uricite	C ₅ H ₄ N ₄ O ₃
Uric acid dihydrate	Uricite	C ₅ H ₄ O ₃ .2H ₂ O
Ammonium urate		NH ₄ C ₅ H ₃ N ₄ O ₃
Sodium acid urate monohydrate		NaC ₅ H ₃ N ₄ O ₃ .H ₂ O
Magnesium ammonium phosphate	Struvite	MgNH ₄ PO ₄ .6H ₂ O
Magnesium acid phosphate trihydrate	Newberyite	MgHPO ₄ .3H ₂ O
Magnesium ammonium phosphate monohydrate	Dittmarite	MgNH ₄ (PO ₄).1H ₂ O
Cystine		[SCH ₂ CH(NH ₂)COOH] ₂
Xanthine		
2,8-Dihydroxyadenine		
Proteins		
Cholesterol		
Calcite		
Potassium urate		
Trimagnesium phosphate		
Melamine		
Matrix		
Drug stones	<ul style="list-style-type: none"> • Active compounds crystallising in urine • Substances impairing urine composition (Section 4.11) 	
Foreign body calculi		

3.1.3 Risk groups for stone formation

The risk status of stone formers is of particular interest because it defines the probability of recurrence or regrowth, and is imperative for pharmacological treatment.

About 50% of recurrent stone formers have just one lifetime recurrence [10, 13]. Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low- or high risk of recurrence (Table 3.1.3) [14, 15].

Table 3.1.3: High-risk stone formers [14-25]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones (CaHPO ₄ ·2H ₂ O)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Nephrocalcinosis
Polycystic kidney disease (PKD)
Gastrointestinal diseases (i.e., jejunio-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery [20]
Sarcoidosis
Spinal cord injury, neurogenic bladder
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drug-induced stone formation (see Table 4.11)
Anatomical abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele
Environmental factors
Chronic lead exposure

3.2 Classification of stones

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence [10, 26-28].

3.2.1 Stone size

Stone size is usually given in one or two dimensions, and stratified into those measuring up to 5, 5-10, 10-20, and > 20 mm in largest diameter.

3.2.2 Stone location

Stones can be classified according to anatomical position: upper, middle or lower calyx; renal pelvis; upper, middle or distal ureter; and urinary bladder. Treatment of bladder stones is not discussed in these guidelines.

3.2.3 X-ray characteristics

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3.2.1), which varies according to mineral composition [28]. Non-contrast-enhanced computed tomography (NCCT) can be used to classify stones according to density, inner structure and composition, which can affect treatment decisions (Section 3.4.1.4.4) [27, 28].

Table 3.2.1: X-ray characteristics

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dihydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-Dihydroxyadenine
		Drug-stones (Section 4.11)

Stratification of stones according to aetiology, composition and risk of recurrence is addressed in Section 3.1.

3.3 Diagnostic evaluation

3.3.1 Diagnostic imaging

The clinical situation will inform on the most appropriate imaging modality, which will differ for a suspected ureteral stone or a suspected renal stone.

Standard evaluation includes a detailed medical history and physical examination. Patients with ureteral stones usually present with loin pain, vomiting, and sometimes fever, but may also be asymptomatic [29].

Ultrasound (US) should be used as the primary diagnostic imaging tool, although pain relief, or any other emergency measures should not be delayed by imaging assessments. Ultrasound is safe (no risk of radiation), reproducible and inexpensive. It can identify stones located in the calices, pelvis, and pyeloureteric and vesicoureteric junctions (US with filled bladder), as well as in patients with upper urinary tract dilatation. Ultrasound has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones [30, 31].

The sensitivity and specificity of KUB (kidney-ureter-bladder radiography) is 44-77% and 80-87%, respectively [32]. Kidney-ureter-bladder radiography should not be performed if NCCT is considered [33]. However, KUB is helpful in differentiating between radiolucent and radiopaque stones and be used for comparison during follow-up.

Recommendation	LE	GR
With fever or solitary kidney, and when diagnosis is doubtful, immediate imaging is indicated.	4	A*

*Upgraded following panel consensus.

3.3.1.1 Evaluation of patients with acute flank pain/suspected ureteral stones

Non-contrast-enhanced computed tomography has become the standard for diagnosing acute flank pain, and has replaced intravenous urography (IVU). Non-contrast-enhanced computed tomography can determine stone diameter and density. When stones are absent, the cause of abdominal pain should be identified. In evaluating patients with suspected acute urolithiasis, NCCT is significantly more accurate than IVU [34].

Recommendation	LE	GR
Following initial ultrasound assessment, use non-contrast-enhanced computed tomography to confirm stone diagnosis in patients with acute flank pain, as it is superior to intravenous urography.	1a	A

Non-contrast-enhanced computed tomography can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [35]. Non-contrast-enhanced computed tomography can determine stone density, inner structure of the stone and skin-to-stone distance and surrounding anatomy; all of which affect selection of treatment modality [28, 36-38]. The advantage of non-contrast imaging must be balanced against loss of information on renal function and urinary collecting system anatomy, as well as higher radiation dose [39-42].

Radiation risk can be reduced by low-dose CT, which may, however, be difficult to introduce in standard clinical practice [43, 44]. In patients with a body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteric stones < 3 mm and 100% for calculi > 3 mm [45]. A meta-analysis of prospective studies [46] has shown that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 96.6% (95% CI: 95.0-97.8) and specificity of 94.9% (95% CI: 92.0-97.0).

Dual-energy CT can differentiate uric acid containing stones from calcium-containing stones [47].

3.3.1.2 Radiological evaluation of patients with renal stones

Intravenous urography can provide information about renal function, the anatomy of the collecting system as well as the level of an obstruction. Non-contrast-enhanced CT allows for rapid 3D data acquisition including information on stone size and density, skin-to-stone distance and surrounding anatomy, but at the cost of increased radiation exposure. Low-dose and ultra-low-dose protocols seem to yield comparable results as standard-dose protocols with the exception of detection of very small stones or stones in obese patients [45, 46].

A small randomised study showed that in supine PNL, pre-operative planning using CT compared to IVU, resulted in easier access and shorter operating times [48].

In case stone removal is planned, the renal collecting system needs to be assessed.

Recommendations	LE	GR
Perform a contrast study if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	3	A*
Use enhanced computed tomography in complex cases because it enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance. Intravenous urography may also be used.	2a	C

*Upgraded based on panel consensus.

3.3.2 Diagnostics - metabolism-related

Each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood besides imaging. At that point, no distinction is made between high- and low-risk patients for stone formation.

Table 3.3.1: Recommendations: basic laboratory analysis - emergency urolithiasis patients
[15, 16, 49, 50]

Recommendations	GR
Urine	
Dipstick test of spot urine sample	A*
<ul style="list-style-type: none"> • red cells • white cells • nitrite • approximate urine pH 	A
Urine microscopy and/or culture	
Blood	
Serum blood sample	A*
<ul style="list-style-type: none"> • creatinine • uric acid • (ionised) calcium • sodium • potassium 	
Blood cell count	
<ul style="list-style-type: none"> • C-reactive protein (CRP) 	
Perform a coagulation test (partial thromboplastin time [PTT] and international normalised ratio [INR]) if intervention is likely or planned.	A*

*Upgraded based on panel consensus.

3.3.2.1 Basic laboratory analysis - non-emergency urolithiasis patients

Biochemical work-up is similar for all stone patients. However, if no intervention is planned, examination of sodium, potassium, C-reactive protein, and blood coagulation time can be omitted.

Only patients at high risk for stone recurrence should undergo a more specific analytical programme [15]. Stone-specific metabolic evaluation is described in Chapter 4.

The easiest method for diagnosing stones is by analysis of a passed stone using a validated method as listed below (see 3.2.2). Once the mineral composition is known, a potential metabolic disorder can be identified.

3.3.2.2 Analysis of stone composition

Stone analysis should be performed in all first-time stone formers.

In clinical practice, repeat stone analysis is needed in the case of:

- recurrence under pharmacological prevention;
- early recurrence after interventional therapy with complete stone clearance;
- late recurrence after a prolonged stone-free period [49, 51].

Patients should be instructed to filter their urine to retrieve a concrement for analysis. Stone passage and restoration of normal renal function should be confirmed.

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) [52-54]. Equivalent results can be obtained by polarisation microscopy. Chemical analysis (wet chemistry) is generally deemed to be obsolete [52].

Recommendations	LE	GR
Perform stone analysis in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).	2	A
Repeat stone analysis in patients: <ul style="list-style-type: none"> • presenting with recurrent stones despite drug therapy; • with early recurrence after complete stone clearance; • with late recurrence after a long stone-free period because stone composition may change. 	2	B

3.3.3 **Diagnosis in special groups and conditions**

3.3.3.1 *Diagnostic imaging during pregnancy*

In pregnant women diagnostic imaging (exposure to ionising radiation) might be associated with teratogenic risks and development of (childhood) malignancies. The risk for the child crucially depends on gestational age and radiation dose delivered. X-ray imaging during the first trimester should be reserved for patients in which alternative imaging methods have failed [55, 56].

Ultrasound (when necessary using change in renal resistive index and transvaginal/transabdominal US with a full bladder) has become the primary radiological diagnostic tool when evaluating pregnant patients suspected of renal colic. However, normal physiological changes in pregnancy can mimic ureteral obstruction [57].

Magnetic resonance imaging (MRI) can be used, as a second-line procedure, to define the level of urinary tract obstruction, and to visualise stones as a filling defect [58, 59].

Low dose CT protocols reduce the radiation exposure and are currently recommended to be used judiciously in pregnant women as a last-line option [60, 61].

Recommendations	LE	GR
Use ultrasound as the preferred method of imaging in pregnant women.	1a	A*
In pregnant women, use magnetic resonance imaging as a second-line imaging modality.	3	C
In pregnant women, use low-dose computed tomography as a last-line option.	3	C

*Upgraded following panel consensus.

3.3.3.2 *Children*

Children with urinary stones have a high risk of recurrence; therefore, standard diagnostic procedures for high-risk patients apply (Section 3.1.3 and Chapter 4). The most common non-metabolic disorders facilitating stone formation are vesicoureteral reflux (VUR), UPJ obstruction, neurogenic bladder, and other voiding difficulties [62].

Summary of evidence	LE
In children, the most common non-metabolic disorders facilitating stone formation are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, and other voiding difficulties [62].	4

3.3.3.2.1 *Diagnostic imaging*

When selecting diagnostic procedures to identify urolithiasis in children, it should be remembered that these patients might be uncooperative, require anaesthesia, and may be sensitive to ionising radiation [63-65]. Again, the principle of ALARA (As Low As Reasonably Achievable) should be observed.

3.3.3.2.2 Ultrasound

Ultrasound is the primary imaging technique [63] in children. Its advantages are absence of radiation and no need for anaesthesia. Imaging should include both the fluid-filled bladder with adjoining portion of the ureters, as well as the upper ureter [66-70].

Colour Doppler US shows differences in the ureteric jet [67] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [68].

Nevertheless, US fails to identify stones in > 40% of children [69-72] (LE: 4), and provides limited information on renal function.

3.3.3.2.3 Plain films (KUB radiography)

KUB radiography can help to identify stones and their radiopacity, and facilitate follow-up.

3.3.3.2.4 Intravenous urography (IVU)

The radiation dose for IVU is comparable to that for voiding cystourethrography (0.33 mSV) [73]. However, the need for contrast medium injection is a major drawback.

3.3.3.2.5 Helical computed tomography (CT)

Recent low-dose CT protocols have been shown to significantly reduce radiation exposure [42, 74].

In children, only 5% of stones escape detection by NCCT [60, 67, 74]. Sedation or anaesthesia is rarely needed with modern high-speed CT equipment.

3.3.3.2.6 Magnetic resonance urography (MRU)

Magnetic resonance urography cannot be used to detect urinary stones. However, it might provide detailed anatomical information about the urinary collecting system, the location of an obstruction or stenosis in the ureter, and renal parenchymal morphology [75].

Recommendations	GR
In all children, complete a metabolic evaluation based on stone analysis.	A
Collect stone material for analysis to classify the stone type.	A*
In children, use ultrasound as first-line imaging modality when a stone is suspected; it should include the kidney, fluid-filled bladder and the ureter next to the kidney and the (filled) bladder.	B
If ultrasound will not provide the required information, perform a kidney-ureter-bladder radiography (or low-dose non-contrast-enhanced computed tomography).	B

*Upgraded following panel consensus.

3.4 Disease management

3.4.1 Management of patients with renal or ureteral stones

Treatment decisions for upper urinary tract calculi are based on several general aspects such as stone composition, stone size, and symptoms.

3.4.1.1 Renal colic

Pain relief

Pain relief is the first therapeutic step in patients with an acute stone episode [76].

Non-steroidal anti-inflammatory drugs (NSAIDs) including metamizole (dipyrone), a pyrazolone NSAID, are effective in patients with acute stone colic [77, 78], and have better analgesic efficacy than opioids. The addition of antispasmodics to NSAIDs does not result in better pain control and data on other types of non-opioid, non-NSAID medication is scarce [79]. Patients receiving NSAIDs are less likely to require further analgesia in the short term. It should be taken into consideration that the use of diclofenac and ibuprofen increased major coronary events. Diclofenac is contraindicated in patients with congestive heart failure (New York Heart Association class II-IV), ischaemic heart disease and peripheral arterial- and cerebrovascular disease. Patients with significant risk factors for cardiovascular events should be treated with diclofenac only after careful consideration. As risks increase with dose and duration, the lowest effective dose should be used for the shortest duration [80, 81].

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs, and carry a greater likelihood of further analgesia being needed [82] (see below). If an opioid is used, it is recommended that it is not pethidine.

Prevention of recurrent renal colic

Facilitation of passage of ureteral stones is discussed in Section 3.4.3.1.2.

For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g., diclofenac sodium, 100-150 mg/day, 3-10 days) may help reduce inflammation and the risk of recurrent pain [83, 84]. Although diclofenac can affect renal function in patients with already reduced function, it has no functional effect in patients with normal renal function [85] (LE: 1a).

In a double-blind, placebo-controlled trial, recurrent pain episodes of stone colic were significantly fewer in patients treated with NSAIDs (as compared to no NSAIDs) during the first seven days of treatment [86]. Contrary to earlier findings, daily α -blockers did not reduce recurrent pain or analgesia requirements in patients with distal ureteral stones in two recent large high-quality studies [87, 88] (Section 3.4.3.1.2). The most recent SR and meta-analysis by Hollingsworth *et al.* [4] addressed pain reduction as a secondary outcome and concluded that MET seems efficacious in reducing pain episodes of patients with ureteric stones who are amenable to conservative management. Patients benefitting most might be those with larger (distal) stones.

If analgesia cannot be achieved medically, drainage, using stenting or percutaneous nephrostomy or stone removal, should be performed.

Recommendations	GR
Provide immediate pain relief in acute stone episodes.	A
Whenever possible, offer a non-steroidal anti-inflammatory as the first drug of choice. e.g. metamizol (dipyrone); alternatively, depending on cardio-vascular risk factors, diclofenac*, indomethacin or ibuprofen**.	A
Offer hydromorphone, pentazocine or tramadol as a second choice.	C

*Affects glomerular filtration rate (GFR) in patients with reduced renal function (LE: 2a).

**Recommended to counteract recurrent pain after ureteral colic.

Summary of evidence	LE
Administration of daily α -blockers seems to reduce colic episodes, although controversy remains in the published literature.	1b
For symptomatic ureteral stones, urgent stone removal as first-line treatment is a feasible option in selected cases (see text).	1b

3.4.1.2 Management of sepsis and/or anuria in obstructed kidney

The obstructed kidney with all signs of urinary tract infection (UTI) and/or anuria is a urological emergency.

Urgent decompression is often necessary to prevent further complications in infected hydronephrosis secondary to stone-induced, unilateral or bilateral renal obstruction.

Decompression

Currently, there are two options for urgent decompression of obstructed collecting systems:

- placement of an indwelling ureteral stent;
- percutaneous placement of a nephrostomy tube.

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting for primary treatment of infected hydronephrosis. There is no good quality evidence to suggest that ureteric stenting has more complications than percutaneous nephrostomy [89, 90].

Only one RCT [91] compared different modalities of decompression of acute infected hydronephrosis. The complications of percutaneous nephrostomy insertion have been reported consistently, but those of ureteric stent insertion are less well described [89]. Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy. A small RCT showed the feasibility of immediate ureteroscopic stone removal combined with appropriate antibiotic regimen; however, at the cost of longer hospital stay and higher analgesic requirements [92].

In children, ureteric stents might have some advantage compared to PCN in case of acute anuria [93].

Summary of evidence	LE
For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.	1b

Recommendations	LE	GR
Urgently decompress the collecting system in case of sepsis with obstructing stones, using percutaneous drainage or ureteral stenting.	1b	A
Delay definitive treatment of the stone until sepsis is resolved.	1b	A

Further measures

Following urgent decompression of the obstructed and infected urinary collecting system, both urine- and blood samples should be sent for culture-antibiogram sensitivity testing, and antibiotics should be initiated immediately thereafter or continued if initiated prior to testing. The regimen should be re-evaluated in the light of the culture-antibiogram test. Although clinically well accepted, the impact of a second antibiogram test on treatment outcome has not yet been evaluated. Intensive care might become necessary [94].

Recommendations	GR
Collect (again) urine for antibiogram test following decompression.	A*
Start antibiotics immediately (+ intensive care if necessary).	
Re-evaluate antibiotic regimen following antibiogram findings.	

*Upgraded based on panel consensus.

3.4.1.3 General recommendations and precautions for stone removal

3.4.1.3.1 Antibiotic therapy

Urinary tract infections should always be treated if stone removal is planned. In patients with clinically significant infection and obstruction, drainage should be performed for several days, via a stent or percutaneous nephrostomy, before starting stone removal.

Recommendation	GR
Obtain a urine culture or perform urinary microscopy before any treatment is planned.	A*

*Upgraded following panel consensus.

Perioperative antibiotic prophylaxis

For prevention of infection following ureteroscopy and percutaneous stone removal, no clear-cut evidence exists [95, 96]. In a review of a large database of patients undergoing percutaneous nephrolithotomy, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of post-operative fever and other complications [97]. Single dose administration was found to be sufficient [98].

Recommendations	LE	GR
Exclude or treat urinary tract infections prior to stone removal.	1b	A
Offer perioperative antibiotic prophylaxis to all patients undergoing endourological treatment.	1b	A*

3.4.1.3.2 Antithrombotic therapy and stone treatment

Patients with a bleeding diathesis, or receiving antithrombotic therapy, should be referred to an internist for appropriate therapeutic measures before deciding on stone management [99-103]. In patients with an uncorrected bleeding diathesis, the following are at elevated risk of haemorrhage or perinephric haematoma (PNH) (high-risk procedures):

- shock wave lithotripsy (SWL) (hazard ratio of PNH up to 4.2 during anticoagulant/antiplatelet medication [104] [LE: 2]);
- percutaneous nephrolithotripsy;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [99, 105, 106].

Shock wave lithotripsy is feasible and safe after correction of the underlying coagulopathy [107-111]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, ureteroscopy (URS), in contrast to SWL and PNL, might offer an alternative approach since it is associated with less morbidity [112-116]. Only data on flexible ureteroscopy are available which support the superiority of URS in the treatment of proximal ureteric stones [113, 117].

Table 3.4.1: Risk stratification for bleeding [101-103, 118]

Low-risk bleeding procedures	Cystoscopy Flexible cystoscopy Ureteral catheterisation Extraction of ureteric stent Ureteroscopy
High-risk bleeding procedures	Shock wave lithotripsy Percutaneous nephrostomy Percutaneous nephrolithotripsy

Table 3.4.2: Suggested strategy for antithrombotic therapy in stone removal [101-103]

(In collaboration with cardiologist/internist weigh the risks and benefits of discontinuation of therapy, vs. delaying elective surgical procedures.)

	Bleeding risk of planned procedure	Risk of thromboembolism		
		Low risk	Intermediate risk	High risk
Warfarin Dabigatran Rivaroxaban Apixaban	Low-risk procedure	May be continued	Bridging therapy	Bridging therapy
	High-risk procedure	May be temporarily discontinued at appropriate interval. Bridging therapy is strongly recommended.	Bridging therapy	Bridging therapy
Aspirin	Low-risk procedure	Continue	Continue	Elective surgery: postpone. Non deferrable surgery: continue
	High-risk procedure	Discontinue	Elective surgery: postpone. Non-deferrable surgery: continue, if is possible.	Elective surgery: postpone. Non-deferrable surgery: continue.
Thienopyridine agents (P2Y12 receptor inhibitors)	Low-risk procedure	Discontinue five days before intervention. Resume within 24-72 hours with a loading dose.	Continue	Elective surgery: postpone. Non-deferrable surgery: continue.
	High-risk procedure	Discontinue five days before intervention and resume within 24-72 hours with a loading dose.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24-72 hours with a loading dose. Bridging therapy - GPIIb/IIIa inhibitors if aspirin is discontinued.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24-72 hours, with a loading dose. Bridging therapy - GPIIb/IIIa inhibitors.

Recommendations	LE	GR
Offer active surveillance to patients at high risk for thrombotic complications in the presence of an asymptomatic calyceal stone.	4	C
Decide on temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, in consultation with the internist.	3	B
Prefer retrograde (flexible) URS if stone removal is essential and antithrombotic therapy cannot be discontinued, since it is associated with less morbidity.	2a	A*

*Upgraded based on panel consensus.

3.4.1.3.3 Obesity

Obesity can cause a higher risk due to anesthesiological requirements, and a lower success rate after SWL and PNL.

3.4.1.3.4 Stone composition

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard as well as stones with high density on NCCT [36]. Percutaneous nephrolithotomy or ureterorenoscopy (RIRS) and URS are alternatives for removal of large SWL-resistant stones.

Recommendations	LE	GR
Consider the stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit (HU) on unenhanced computed tomography (CT). Stones with density > 1,000 HU on non-contrast-enhanced CT are less likely to be disintegrated by shock wave lithotripsy.	2-4	B*
Attempt to dissolve radiolucent stones (See Section 3.4.2.1.2.2).	2a	B

*Upgraded in parts based on panel consensus.

3.4.1.3.5 Steinstrasse

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter, may interfere with the passage of urine [119]. Steinstrasse occurs in 4-7% cases of SWL [120], and the major factor in the development of steinstrasse formation is stone size [121].

A major problem of steinstrasse is ureteral obstruction, which may be silent in up to 23% of cases. A meta-analysis including eight RCTs (n = 876) suggests a benefit of stenting before SWL in terms of steinstrasse formation, but does not result in a benefit on stone-free rates (SFRs) or less auxiliary treatments [122-124].

When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy significantly increases stone expulsion and reduces the need for endoscopic intervention [125, 126].

Summary of evidence	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse [125].	1b
When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.	4
Shock wave lithotripsy is indicated in asymptomatic and symptomatic cases, with no evidence of urinary tract infection (UTI), when large stone fragments are present [127].	4
Ureterorenoscopy is effective for the treatment of steinstrasse [128].	3
Placement of a percutaneous nephrostomy tube or ureteral stent is indicated for symptomatic ureteric obstruction with/without urinary tract infection.	4

Recommendations	LE	GR
Treat steinstrasse associated with urinary tract infection/fever preferably with percutaneous nephrostomy.	4	C
Treat steinstrasse when large stone fragments are present with shock wave lithotripsy or ureterorenoscopy.	4	C

3.4.2 Specific stone management in renal stones

The natural history of small, non-obstructing asymptomatic calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, timing and type of intervention. Treatment options are chemolysis or active stone removal.

3.4.2.1 Types of treatments

3.4.2.1.1 Conservative treatment (Observation)

Observation of renal stones, especially in calices, depends on their natural history (Section 3.4.2.2). The recommendations provided are not supported by high level literature. There is a prospective trial supporting annual observation for asymptomatic inferior calyceal stones, ≤ 10 mm. In case stone growth is detected the follow up interval should be lowered. Intervention is advised for stones growing > 5 mm [129].

Summary of evidence	LE
It is still debatable whether renal stones should be treated, or whether annual follow-up is sufficient for asymptomatic calyceal stones that have remained stable for six months.	4

Recommendation	GR
Follow-up periodically in cases where renal stones are not treated (initially after six months then yearly, evaluating symptoms and stone status [either by ultrasound, kidney-ureter-bladder radiography or computed tomography]).	A*

*Upgraded based on panel consensus.

3.4.2.1.2 Chemolysis

3.4.2.1.2.1 Percutaneous irrigation chemolysis

Percutaneous chemolysis is rarely used nowadays. Percutaneous irrigation chemolysis may be an option for infection- and uric acid stones [130, 131]. For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5-4) can be used [132].

3.4.2.1.2.2 Oral chemolysis

Stones composed of uric acid, but not sodium or ammonium urate, can be dissolved by oral chemolysis. Prior stone analysis may provide information on stone composition. Urinary pH measurement and X-ray characteristics can provide information on the type of stone.

Oral chemolitholysis is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate [131, 133]. The pH should be adjusted to 7.0-7.2. Chemolysis is more effective at a higher pH, which might, however, promote calcium phosphate stone formation. Monitoring of radiolucent stones during therapy is the domain of US; however, repeat-NCCT might be necessary.

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated [134]. A combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones [134].

Recommendations	GR
Inform the patient how to modify the dosage of alkalinising medication according to urine pH, which is a direct consequence of such medication.	A
Inform the patient how to monitor urine pH by dipstick three times a day (at regular intervals). Morning urine must be included.	A
Carefully monitor radiolucent stones during/after therapy.	A*
Inform the patient of the significance of compliance.	A

*Upgraded based on panel consensus.

3.4.2.1.3 Extracorporeal shock wave lithotripsy (SWL)

Success depends on the efficacy of the lithotripter and the following factors:

- size, location (ureteral, pelvic or calyceal), and composition (hardness) of the stones (Section 3.4.3.2);
- patient's habitus (Section 3.4.2.2);
- performance of SWL (best practice, see below).

Each of these factors significantly influence retreatment rate and final outcome of SWL.

3.4.2.1.3.1 Contraindications of extracorporeal shock wave lithotripsy

There are several contraindications to the use of extracorporeal SWL, including:

- pregnancy, due to the potential effects on the foetus [135];
- bleeding diatheses, which should be compensated for at least 24 hours before and 48 hours after treatment [136];
- uncontrolled UTIs;

- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [137];
- anatomical obstruction distal to the stone.

3.4.2.1.3.2 Best clinical practice

Stenting

Routine use of internal stents before SWL does not improve SFRs, nor lowers the number of auxiliary treatments. It may, however, reduce formation of steinstrasse [122, 124] (LE: 1b).

Pacemaker

Patients with a pacemaker can be treated with SWL, provided that appropriate technical precautions are taken; patients with implanted cardioverter defibrillators must be managed with special care (firing mode temporarily reprogrammed during SWL treatment). However, this might not be necessary with new-generation lithotripters [138].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFRs [139-144]. Tissue damage increases with shock wave frequency [145-150].

Number of shock waves, energy setting and repeat treatment sessions

The number of shock waves that can be delivered at each session depends on the type of lithotripter and shock wave power. There is no consensus on the maximum number of shock waves.

Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment [147], which prevents renal injury [151-153]. Animal studies [154] and a prospective randomised study [155] have shown better SFRs (96% vs. 72%) using stepwise power ramping, but no difference has been found for fragmentation or evidence of complications after SWL, irrespective of whether ramping was used [156].

There are no conclusive data on the intervals required between repeated SWL sessions. However, clinical experience indicates that repeat sessions are feasible (within 1 day for ureteral stones).

Summary of evidence	LE
Stepwise power ramping prevents renal injury.	1b
Clinical experience has shown that repeat sessions are feasible (within one day for ureteral stones).	4
Optimal shock wave frequency is 1.0 to 1.5Hz.	1a

Improvement of acoustic coupling

Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important.

Defects (air pockets) in the coupling gel deflect 99% of shock waves [157]. Ultrasound gel is probably the most widely used agent available for use as a lithotripsy coupling agent [158].

Recommendation	LE	GR
Ensure correct use of the coupling agent because this is crucial for effective shock wave transportation.	2a	B

Procedural control

Results of treatment are operator dependent, and better results are obtained by experienced clinicians. During the procedure, careful imaging control of localisation contributes to outcome quality [159].

Recommendation	LE	GR
Maintain careful fluoroscopic and/or ultrasonographic monitoring during shock wave lithotripsy.	3	A*

*Upgraded based on panel consensus.

Pain control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [160-162].

Recommendation	LE	GR
Use proper analgesia because it improves treatment results by limiting pain-induced movements and excessive respiratory excursions.	4	C

Antibiotic prophylaxis

No standard antibiotic prophylaxis before SWL is recommended. However, prophylaxis is recommended in the case of internal stent placement ahead of anticipated treatments and in the presence of increased bacterial burden (e.g., indwelling catheter, nephrostomy tube, or infectious stones) [50, 163, 164].

Recommendation	LE	GR
In the case of infected stones or bacteriuria, prescribe antibiotics prior to shock wave lithotripsy.	4	C

Medical therapy after extracorporeal shock wave lithotripsy

In spite of conflicting results, most RCTs and several meta-analyses support MET after SWL for ureteral or renal stones as adjunct to expedite expulsion and to increase SFRs. Medical expulsion therapy might also reduce analgesic requirements [165-172].

3.4.2.1.3.3 Complications of extracorporeal shock wave lithotripsy

Compared to PNL and URS, there are fewer overall complications with SWL [173, 174] (Table 3.4.1).

Table 3.4.1: Shock wave lithotripsy-related complications [120, 175-188]

Complications		%	Ref.	
Related to stone fragments	Steinstrasse	4 - 7	[120, 175, 176]	
	Regrowth of residual fragments	21 - 59	[177, 178]	
	Renal colic	2 - 4	[179]	
Infectious	Bacteriuria in non-infection stones	7.7 - 23	[177, 180]	
	Sepsis	1 - 2.7	[177, 180]	
Tissue effect	Renal	Haematoma, symptomatic	< 1	[181]
		Haematoma, asymptomatic	4 - 19	[181]
	Cardiovascular	Dysrhythmia	11 - 59	[177, 182]
		Morbid cardiac events	Case reports	[177, 182]
	Gastrointestinal	Bowel perforation	Case reports	[183-185]
		Liver, spleen haematoma	Case reports	[15-188]

The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory; however, no evidence exists supporting the hypothesis that SWL may cause long-term adverse effects [189-194].

3.4.2.1.4 Endourology techniques for renal stone removal

3.4.2.1.4.1 Percutaneous nephrolithotomy (PNL)

Percutaneous nephrolithotripsy remains the standard procedure for large renal calculi. Different rigid and flexible endoscopes are available and the selection is mainly based on the surgeon's own preference. Standard access tracts are 24-30 F. Smaller access sheaths, < 18 French, were initially introduced for paediatric use, but are now increasingly popular in adults.

The efficacy of miniaturised systems seems to be high, but longer operation times apply and benefit compared to standard PNL for selected patients has yet to be demonstrated [195]. There is some evidence that smaller tracts cause less bleeding complications, but further studies need to evaluate this issue. Smaller instruments bear the risk of increasing intra-renal pelvic pressure [5, 196-198].

3.4.2.1.4.1.1 Contraindications

Patients receiving anticoagulant therapy must be monitored carefully pre- and post-operatively. Anticoagulant therapy must be discontinued before PNL [112].

Other important contraindications include:

- untreated UTI;

- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.3.1).

3.4.2.1.4.1.2 Best clinical practice

Intracorporeal lithotripsy

Several methods for intracorporeal lithotripsy are available (devices are discussed in Section 3.4.1.2.1.1.5).

During PNL, ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy. When using miniaturised instruments, laser lithotripsy is associated with lower stone migration than with pneumatic lithotripsy [199]. Flexible endoscopes require laser lithotripsy to maintain tip deflection and the Ho:YAG laser has become the standard [200].

Recommendation	GR
Use ultrasonic, ballistic and holmium: yttrium-aluminium-garnet devices for intracorporeal lithotripsy during percutaneous nephrolithotomy.	A*

**Upgraded based on panel consensus.*

Pre-operative imaging

Pre-procedural evaluations are summarised in Section 3.3.1. In particular, PNL, US or CT of the kidney and the surrounding structures can provide information regarding interpositioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung) [201].

Recommendation	GR
Perform pre-procedural imaging, including contrast medium where possible or retrograde study when starting the procedure, to assess stone comprehensiveness and anatomy of the collecting system to ensure safe access to the renal stone.	A*

**Upgraded based on panel consensus.*

For antibiotic therapy - see General recommendations and precautions for stone removal (Section 3.4.1.4.1).

Positioning of the patient

Both prone and supine positions are equally safe.

Although the supine position confers some advantages, it depends on appropriate equipment being available to position the patient correctly, for example, X-ray devices and an operating table. Most studies cannot demonstrate an advantage of supine PNL in terms of operating room (OR) time. In some series, SFR is lower than for the prone position despite a longer OR time. Prone position offers more options for puncture and is therefore preferred for upper pole or multiple access [202-204]. On the other hand, supine position allows simultaneous retrograde access to the collecting system, using flexible ureteroscope [205]. The Urolithiasis Guidelines Panel aim to set up a SR to assess this topic.

Puncture

Although fluoroscopy is the most common intra-operative imaging method, the (additional) use of US reduces the radiation exposure.

Colon interposition in the access tract of PNL can lead to colon injuries. Pre-operative CT or intra-operative US allows identification of the tissue between the skin and kidney and lowers the incidence of bowel injury. The calyceal puncture may be done under direct visualisation using simultaneous flexible ureterorenoscopy [206-209].

Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a balloon dilatator. Although there are papers demonstrating that single step dilation is equally effective as other methods, the difference in outcomes is most likely related to surgeon experience rather than to the technology used [210].

Choice of instruments

The Urolithiasis Panel performed a SR assessing the outcomes of PNL using smaller tract sizes (< 22 Fr, mini-PNL) for removing renal calculi [5]. Stone-free rates were comparable in miniaturised and standard PNL

procedures. Procedures performed with small instruments tended to be associated with significantly lower blood loss, while the duration of procedure tended to be significantly longer. Other complications were not notably different between PNL types. However, the quality of the evidence was poor, drawn mainly from small studies, the majority of which were single-arm case series, and only two of which were RCTs. Furthermore, the tract sizes used, and types of stones treated were heterogeneous. Hence, the risk of bias and confounding were high.

Nephrostomy and stents

The decision on whether or not to place a nephrostomy tube at the end of the PNL procedure depends on several factors, including:

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intra-operative blood loss;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones;
- solitary kidney;
- bleeding diathesis;
- planned percutaneous chemolitholysis.

Small bore nephrostomies seem to have advantages in terms of post-operative pain [211, 212]. Tubeless PNL is performed without a nephrostomy tube. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as totally tubeless PNL. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [213-215].

Recommendation	LE	GR
In uncomplicated cases, perform a tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) percutaneous nephrolithotomy procedure as it is a safe alternative.	1b	A

3.4.2.1.4.1.3 Complications

The most common post-operative complications associated with PNL are fever and bleeding, urinary leakage, and problems due to residual stones (Table 3.4.2).

Table 3.4.2: Complications following percutaneous nephrolithotomy [216]

Complications	Trans-fusion	Embolisation	Urinoma	Fever	Sepsis	Thoracic complication	Organ injury	Death	LE
(Range)	(0-20%)	(0-1.5%)	(0-1%)	(0-32.1%)	(0.3-1.1%)	(0-11.6%)	(0-1.7%)	(0-0.3%)	1a
N = 11,929	7%	0.4%	0.2%	10.8%	0.5%	1.5%	0.4%	0.05%	

Peri-operative fever can occur, even with a sterile pre-operative urinary culture and peri-operative antibiotic prophylaxis, because the renal stones themselves may be a source of infection. Intra-operative renal stone culture may therefore help to select post-operative antibiotics [217, 218]. Intra-operative irrigation pressure < 30 mmHg and unobstructed post-operative urinary drainage may be important factors in preventing post-operative sepsis. Bleeding after PNL may be treated by brief clamping of the nephrostomy tube. Super-selective embolic occlusion of the arterial branch may become necessary in the case of severe bleeding.

3.4.2.1.4.2 Ureterorenoscopy for renal stones (RIRS)

Technical improvements including endoscope miniaturisation, improved deflection mechanism, enhanced optical quality and tools, and introduction of disposables have led to an increased use of URS for both, renal and ureteral stones. Major technological progress has been achieved for RIRS. A recent SR addressing renal stones > 2 cm showed a cumulative SFR of 91% with 1.45 procedures/patient; 4.5% of the complications were ≥ Clavien 3 [219-221]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [220, 222, 223]. For best clinical practice see Section 3.4.3.1.4.1.2 - Ureteral stones-URS.

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones that need disintegration within the lower renal pole, it may help to displace them into a more accessible calyx [224].

Recommendation	GR
Use flexible ureterorenoscopy in case percutaneous nephrolithotomy or shock wave lithotripsy are not an option (even for stones > 2 cm). However, in that case there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed. In complex stone cases, use open or laparoscopic approaches as possible alternatives.	B

3.4.2.1.4.3 Open and laparoscopic surgery for removal of renal stones

Advances in SWL and endourological surgery (URS and PNL) have significantly decreased the indications for open or laparoscopic stone surgery [225-231]. There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PNL. Additionally, a combined approach with PNL and RIRS may also be an appropriate alternative. However, if a reasonable number of percutaneous approaches are not likely to be successful, or if multiple, endourological approaches have been performed unsuccessfully; open or laparoscopic surgery may be a valid treatment option [232-239].

Recommendations	LE	GR
Offer laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, (flexible) ureterorenoscopy and percutaneous nephrolithotomy fail, or are unlikely to be successful.	3	C
When expertise is available, perform surgery laparoscopically before proceeding to open surgery, especially when the stone mass is centrally located.	3	C

3.4.2.2 Indication for active stone removal of renal stones [240]

- stone growth;
- stones in high-risk patients for stone formation;
- obstruction caused by stones;
- infection;
- symptomatic stones (e.g., pain or haematuria);
- stones > 15 mm;
- stones < 15 mm if observation is not the option of choice.
- patient preference;
- comorbidity;
- social situation of the patient (e.g., profession or travelling);
- choice of treatment.

The risk of a symptomatic episode or need for intervention of patients with asymptomatic renal stones seems to be ~10-25% per year, with a cumulative five-year event probability of 48.5% [129, 241, 242]. A prospective RCT with > 2 year clinical follow-up reported no significant difference between SWL and observation when comparing asymptomatic calyceal stones < 15 mm in terms of SFR, symptoms, requirement for additional treatment, quality of life (QoL), renal function, or hospital admission [243]. Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported [242, 244, 245]. In a follow-up period of almost five years after SWL, two series have demonstrated that up to 25% of patients with small residual fragments needed treatment [178, 246]. Although the question of whether calyceal stones should be treated is still unanswered, stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain are indications for treatment [240, 247, 248].

Summary of evidence	LE
Although the question of whether calyceal stones should be treated is still unanswered, stone growth, <i>de novo</i> obstruction, associated infection, and acute and/or chronic pain are indications for treatment.	3

Recommendations	GR
Offer active treatment for renal stones in case of stone growth, <i>de novo</i> obstruction, associated infection, and acute and/or chronic pain.	C
Assess comorbidity and patient preference when making treatment decisions.	C

3.4.2.3 Selection of procedure for active removal of renal stones

For general recommendations and precautions see Section 3.4.1.3.

3.4.2.3.1 Stones in renal pelvis or upper/middle calices

Shock wave lithotripsy, PNL and RIRS are available treatment modalities for renal calculi. While PNL efficacy is hardly affected by stone size, the SFRs after SWL or URS are inversely proportional to stone size [249-252]. Shock wave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [251, 253, 254]. Endourology is considered an alternative because of the reduced need of repeated procedures and consequently a shorter time until stone-free status is achieved. Stones > 20 mm should be treated primarily by PNL, because SWL often requires multiple treatments, and is associated with an increased risk of ureteral obstruction (colic or steinstrasse) with a need for adjunctive procedures (Figure 3.4.1) [173]. Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm in uncomplicated cases as SFRs decrease, and staged procedures will be required [255-257]. However, it may be a first-line option in patients where PNL is not an option or contraindicated.

3.4.2.3.2 Stones in the lower renal pole

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other intra-renal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25-95%. The preferential use of endoscopic procedures is supported by some current reports, even for stones smaller than 1 cm [173, 249, 250, 252, 253, 257-265].

The following can impair successful stone treatment by SWL [260, 266-269]:

- steep infundibular-pelvic angle;
- long calyx;
- long skin-to-stone distance;
- narrow infundibulum (Table 3.4.4).

Further anatomical parameters cannot yet be established. Supportive measures such as inversion, vibration or hydration may facilitate stone clearance [270].

Table 3.4.4: Unfavourable factors for shock wave lithotripsy success for lower calyceal stones
[260, 266, 271]

Factors that make shock wave lithotripsy less likely
Shock wave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).
Steep infundibular-pelvic angle.
Long lower pole calyx (> 10 mm).
Narrow infundibulum (< 5 mm).
Long skin-to-stone distance (> 10 cm).

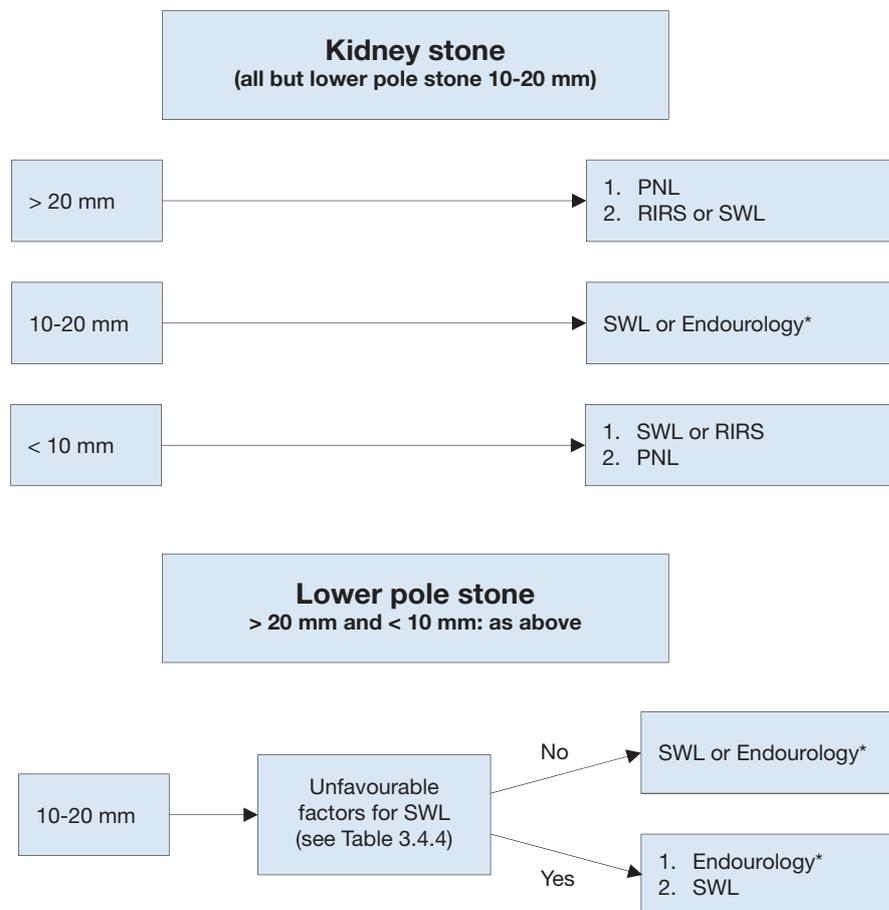
If there are negative predictors for SWL, PNL and RIRS might be reasonable alternatives, even for smaller calculi [258]. Retrograde renal surgery seems to have comparable efficacy to SWL [173, 253]. Recent clinical experience has suggested a higher SFR of RIRS compared to SWL, but at the expense of greater invasiveness. Depending on operator skills, stones up to 3 cm can be treated by RIRS [221, 272-274]. However, staged procedures are frequently required.

In complex stone cases, open or laparoscopic approaches are possible alternatives (see appropriate chapters).

3.4.2.3.3 Recommendations for the selection of procedures for active removal of renal stones

Recommendations	GR
Offer shock wave lithotripsy (SWL) and endourology (percutaneous nephrolithotomy [PNL], retrograde renal surgery [RIRS]) as treatment options for stones < 2 cm within the renal pelvis and upper or middle calices.	B
Perform PNL as first-line treatment of larger stones > 2 cm.	B
In case PNL is not an option, treat larger stones (> 2 cm) with flexible ureterorenoscopy or SWL. However, in such instances there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	B
For the lower pole, perform PNL or RIRS, even for stones > 1 cm, as the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	B

Figure 3.4.1: Treatment algorithm for renal calculi



*The term 'Endourology' encompasses all PNL and URS interventions.

PNL = percutaneous nephrolithotomy; RIRS = retrograde renal surgery; SWL = shock wave lithotripsy; URS = ureterorenoscopy.

3.4.3 Specific stone management of Ureteral stones

3.4.3.1 Types of treatment

3.4.3.1.1 Conservative treatment/observation

There are only limited data regarding spontaneous stone passage according to stone size [275]. It is estimated that 95% of stones up to 4 mm pass within 40 days [189].

Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).

Recommendations	LE	GR
In patients with newly diagnosed small* ureteral stones, if active removal is not indicated (Section 3.4.2.2), observe patient initially with periodic evaluation.	1a	A
Offer patient appropriate medical therapy to facilitate stone passage during observation.		

*See stratification data [189].

Based on the analysis of available evidence, an exact cut-off size for stones that are likely to pass spontaneously cannot be provided; < 10 mm may be considered a best estimate [189]. Therefore, the Panel decided not to include stone size but rather recommend “small”, suggesting < 6 mm. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

3.4.3.1.2 Pharmacological treatment, Medical expulsive therapy

Medical expulsive therapy (MET) should only be used in informed patients. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). Several substances are in discussion for MET [276-279]. When using α -blockers for MET possible side effects include retrograde ejaculation and hypotension [84].

Meta-analyses have shown that patients with ureteral stones treated with α -blockers or nifedipine are more likely to pass stones with fewer colic episodes than those not receiving such therapy [84, 280]. However, there is contradictory evidence between these studies and several well-designed, multicentre, placebo-controlled, double-blinded randomised studies showing limited, or no, benefit using α -blockers, besides some advantage for distal ureteral stones > 5 mm) [87, 88, 281]. A published meta-analysis, including 55 trials with a data search cut-off of July 1st 2015, also including the publications addressed above, assessed stone passage as primary outcome [4]. Based on the well-designed sensitivity analyses of this meta-analysis, α -blockers promote spontaneous stone expulsion of large stones located in any part of the ureter.

The panel concludes that MET seems efficacious in the treatment of patients with ureteric stones who are amenable to conservative management. The greatest benefit might be among those with larger (distal) stones [282].

Summary of evidence	LE
MET seems to be efficacious treating patients with ureteric stones who are amenable to conservative management. The greatest benefit might be among those with larger (distal) stones.	1a

Based on studies with a limited number of patients [279, 283, 284] (LE: 1b), no recommendation for the use of corticosteroids in combination with α -blockers in MET can be made.

Summary of evidence	LE
There is no evidence to support the use of corticosteroids as monotherapy for MET.	1b
Insufficient data exist to support the use of corticosteroids in combination with α -blockers as an accelerating adjunct.	2a

Recommendations	LE	GR
Select patients for an attempt at spontaneous passage or medical expulsive therapy (MET), based on well-controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve.	4	C
Offer α -blockers as MET as one of the treatment options, in particular for (distal) ureteral stones > 5 mm.	1a	A
Counsel patients regarding the controversies in the literature, attendant risks of MET, including associated drug side effects. Inform the patient that α -blockers as MET are administered off-label ^{†**} .	1b	A*
Follow-up patients in short intervals to monitor stone position and assess for hydronephrosis.	4	A*

[†] It is not known if tamsulosin harms the human foetus or if it is found in breast milk.

*Upgraded based on panel consensus.

**MET in children cannot be recommended due to the limited data in this specific population.

Medical expulsive therapy in special situations is addressed in the particular chapters

3.4.3.1.2.1 Duration of medical expulsive therapy treatment

Most studies have had a duration of one month. No data are currently available to support other time-intervals.

3.4.3.1.3 Shock wave lithotripsy

For best clinical practice, see Section 3.4.2.1.4.1.2 (Renal stones).

Stenting

The stenting is not recommended as part of SWL, since it does not increase SFRs [189, 285]. When a stent is inserted, patients often suffer from frequency, dysuria, urgency, and suprapubic pain [285].

Recommendation	LE	GR
Do not routinely use a stent as part of shock wave lithotripsy treatment of ureteral stones.	1b	A

3.4.3.1.4 Endourology techniques

3.4.3.1.4.1 Ureterorenoscopy

The current standard for rigid ureterorenoscopes are tip diameters of < 8 F. Rigid URS can be used for the whole ureter [189]. However, technical improvements, as well as the availability of digital scopes also favour the use of flexible ureteroscopes in the ureter [219].

3.4.3.1.4.1.1 Contraindications

Apart from general problems, for example, with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

3.4.3.1.4.1.2 Best clinical practice in ureterorenoscopy (URS)

Access to the upper urinary tract

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible. Intravenous sedation is suitable for female patients with distal ureteral stones [286].

Antegrade URS is an option for large, impacted proximal ureteral calculi [287] (Section 3.4.3.1.4.2).

Safety aspects

Fluoroscopic equipment must be available in the OR. We recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [288-290].

Balloon and plastic dilators should be available, if necessary.

Prior rigid ureterorenoscopy can be helpful for optical dilatation followed by flexible URS, if necessary. If ureteral access is not possible, insertion of a JJ stent followed by URS after seven to fourteen days offers an alternative procedure. Bilateral URS during the same session is feasible resulting in similar SFRs, but slightly higher overall (mostly minor) complication rates [291].

Ureteral access sheaths

Hydrophilic-coated ureteral access sheaths, which are available in different calibres (inner diameter from 9 F upwards), can be inserted via a guide wire, with the tip placed in the proximal ureter.

Ureteral access sheaths allow easy, multiple, access to the upper urinary tract and therefore significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreasing intra-renal pressure, and potentially reduces operating time [292, 293].

The insertion of ureteral access sheaths may lead to ureteral damage, whereas the risk is lowest in pre-stented systems [294]. No data on long-term side effects are available [294, 295]. Use of ureteral access sheaths depends on the surgeon's preference.

Stone extraction

The aim of URS is complete stone removal. "Dust and go" strategies should be limited to the treatment of large (renal) stones.

Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [296].

Recommendation	LE	GR
Do not perform stone extraction using a basket without endoscopic visualisation of the stone (blind basketing).	4	A*

*Upgraded based on panel consensus.

Intracorporeal lithotripsy

The most effective lithotripsy system is the Ho:YAG laser, which is currently the optimum standard for ureteroscopy and flexible nephroscopy (Section 3.4.2.1.4.1.2), because it is effective in all stone types [297, 298]. Pneumatic and US systems can be used with high disintegration efficacy in rigid URS [299, 300].

However, stone migration into the kidney is a common problem, which can be prevented by placement of special anti-migration tools proximal of the stone [301]. Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes [302] (LE: 1b).

Recommendation	LE	GR
Use holmium: yttrium-aluminium-garnet laser lithotripsy for (flexible) ureterorenoscopy.	3	B

Stenting before and after URS

Routine stenting is not necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces intra-operative complications [303, 304].

Randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary; stenting might be associated with higher post-operative morbidity [305-307]. A ureteric catheter with a shorter indwelling time (one day) may also be used, with similar results [308].

Stents should be inserted in patients who are at increased risk of complications (e.g., ureteral trauma, residual fragments, bleeding, perforation, UTIs, or pregnancy), and in all doubtful cases, to avoid stressful emergencies. The ideal duration of stenting is not known. Most urologists favour 1-2 weeks after URS. Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability [309, 310]. A recently published meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin [311].

Medical expulsive therapy after ureterorenoscopy

Medical expulsion therapy following Ho:YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic [302] (LE: 1b).

Summary of evidence	LE
In uncomplicated ureterorenoscopy (URS), a stent need not be inserted.	1a
In URS (in particular for renal stones), pre-stenting has been shown to improve outcome.	1b
An α -blocker can reduce stent-related symptoms and colic episodes.	1b

3.4.3.1.4.1.3 Complications

The overall complication rate after URS is 9-25% [189, 312, 313]. Most are minor and do not require intervention. Ureteral avulsion and strictures are rare (< 1%). Previous perforations are the most important risk factor for complications.

3.4.3.1.4.2 Percutaneous antegrade ureterorenoscopy

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i.e. large, impacted proximal ureteral calculi with dilated renal collecting system [314], or when the ureter is not amenable to retrograde manipulation [287, 315-318].

Recommendation	GR
Use percutaneous antegrade removal of ureteral stones as an alternative when shock wave lithotripsy is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde ureterorenoscopy.	A

3.4.3.1.5 Laparoscopic ureteral stone removal

Few studies have reported laparoscopic stone removal (Section 3.4.2.1.4.3). These procedures are usually reserved for special cases. When expertise is available, laparoscopic ureterolithotomy can be performed for large proximal ureteral stones as an alternative to URS or SWL [319, 320]. These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates [234].

Recommendation	LE	GR
For ureterolithotomy, perform laparoscopy for large impacted stones when endoscopic lithotripsy or shock wave lithotripsy has failed.	2	B

3.4.3.2 Indications for active removal of ureteral stones [189, 275, 321]

Indications for active removal of ureteral stones are:

- stones with a low likelihood of spontaneous passage;
- persistent pain despite adequate analgesic medication;
- persistent obstruction;
- renal insufficiency (renal failure, bilateral obstruction, or single kidney).

For general recommendations and precautions see Section 3.4.1.3.

Obesity can cause a lower success rate after SWL and PNL and may influence the choice of treatment.

Summary of evidence	LE
In the case of severe obesity, ureterorenoscopy is a more promising therapeutic option than shock wave lithotripsy.	2b

3.4.3.2.5.1 Bleeding disorder

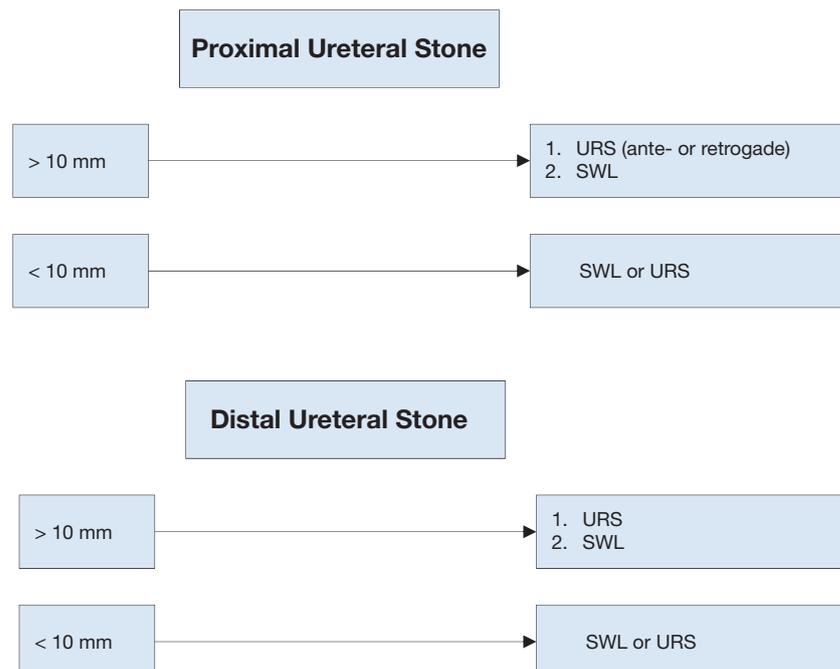
Ureterorenoscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (see also Section 3.4.1.3) [112, 115].

3.4.3.3 Selection of procedure for active removal of ureteral stones

Overall SFRs after URS or SWL for ureteral stones are comparable. However, larger stones achieve earlier stone-free status with URS. Although URS is effective for ureteric calculi, it has greater potential for complications. However, in the current endourological era, the complication rate and morbidity of ureterorenoscopy have been significantly reduced [322]. It has been demonstrated that URS is a safe option in obese patients (BMI > 30 kg/m²) with comparable SFRs and complication rates. However, in morbidly obese patients (BMI > 35 kg/m²) the overall complication rates double [323].

The Panel performed an SR to assess the benefits and harms of URS compared to SWL [6]. Compared with SWL, URS was associated with a significantly greater SFR up to four weeks, but the difference was not significant at three months in the included studies. Ureterorenoscopy was associated with fewer re-treatments and need for secondary procedures, but with a higher need for adjunctive procedures, greater complication rates and longer hospital stay. Counterbalancing for URS's higher SFRs, SWL is associated with least morbidity. Clavien-Dindo grade complications were, if reported, less frequent in patients treated with SWL.

Figure 3.4.2: Treatment algorithm for ureteral calculi (if indicated for active stone removal) (GR: A*)



*Upgraded following panel consensus.

SWL = shock wave lithotripsy; URS = ureterorenoscopy.

Summary of evidence	LE
In obese patients ureterorenoscopy (URS) is a safe and efficient option to remove renal stones.	2b
Ureterorenoscopy in morbidly obese patients have significantly higher complication rates as compared to normal weight patients.	1a

Recommendations	GR
Inform patients that ureterorenoscopy (URS) has a better chance of achieving stone-free status with a single procedure.	A
Inform patients that URS has higher complication rate when compared to shock wave lithotripsy.	A

3.4.4 Management of patients with residual stones

The clinical problem of residual renal stones is related to the risk of developing:

- new stones from such nidi (heterogeneous nucleation);
- persistent UTI;
- dislocation of fragments with/without obstruction and symptoms [178, 324, 325].

Recommendations	LE	GR
Identify biochemical risk factors and offer appropriate stone prevention to patients with residual fragments or stones [178, 325, 326].	1b	A
Follow-up patients with residual fragments or stones regularly to monitor disease course.	4	C

Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones [326]. For all stone compositions, 21-59% of patients with residual stones required treatment within five years. Fragments > 5 mm are more likely than smaller ones to require intervention [178, 324, 327]. There is evidence that fragments > 2 mm are more likely to grow, although this is not associated with increased re-intervention rates at one year follow up [328].

3.4.4.1 Therapy

The indications for active removal of residual stones and selection of the procedure are based on the same criteria as for primary stone treatment (Section 3.4.2.4) and includes repeat SWL [329].

If intervention is not required, medical therapy according to stone analysis, patient risk group, and metabolic evaluation might help to prevent regrowth of residual fragments [330-332].

Summary of evidence	LE
For well-disintegrated stone material in the lower calix, an inversion therapy with simultaneous mechanical percussion manoeuvre under enforced diuresis may facilitate stone clearance [270].	1b

Recommendation	LE	GR
After shock wave lithotripsy and ureterorenoscopy, and in the presence of residual fragments, offer medical expulsive therapy using an α -blocker to improve fragment clearance.	1a	A

Table 3.4.5: Recommendations for the treatment of residual fragments

Residual fragments, stones (largest diameter)	Symptomatic residuals	Asymptomatic residuals	LE	GR
< 4-5 mm	Stone removal	Reasonable follow-up (dependent on risk factors)	4	C
> 5 mm	Stone removal		4	C

3.4.5 Management of specific patient groups

3.4.5.1 Management of urinary stones and related problems during pregnancy

Clinical management of a pregnant urolithiasis patient is complex and demands close collaboration between patient, radiologist, obstetrician and urologist. For diagnostic imaging see Section 3.3.1.

If spontaneous passage does not occur, or if complications develop (e.g., induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary [333-335]. Unfortunately, these

temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation. Ureteroscopy has become a reasonable alternative in these situations [336-338]. Although feasible, retrograde endoscopic and percutaneous removal of renal stones during pregnancy remain an individual decision and should be performed only in experienced centres [339].

Pregnancy remains an absolute contraindication for SWL.

Summary of evidence	LE
If intervention becomes necessary, placement of a ureteral stent or a percutaneous nephrostomy tube is a readily available primary option.	3
Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage.	1a
Regular follow-up until final stone removal is necessary due to the higher encrustation tendency of stents during pregnancy.	

Recommendation	GR
Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except those that have clinical indications for intervention).	A

3.4.5.2 Management of stones in patients with urinary diversion

3.4.5.2.1 Aetiology

Patients with urinary diversion are at high risk for stone formation in the renal collecting system and ureter or in the conduit or continent reservoir [340-342]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [343] (Section 3.1.3). One study has shown that the risk for recurrent upper-tract stones in patients with urinary diversion subjected to PNL was 63% at five years [344].

3.4.5.2.2 Management

Smaller upper-tract stones can be treated effectively with SWL [316, 345]. In the majority, endourological techniques are necessary to achieve stone-free status [315]. In individuals with long, tortuous conduits or with invisible ureter orifices, a retrograde endoscopic approach might be difficult or impossible.

Summary of evidence	LE
The choice of access depends on the feasibility of orifice identification in the conduit or bowel reservoir. Whenever a retrograde approach is impossible, percutaneous access with antegrade ureteroscopy is the alternative.	4

Recommendation	GR
Perform percutaneous lithotomy to remove large renal stones in patients with urinary diversion, as well as for ureteral stones that cannot be accessed via a retrograde approach, or that are not amenable to shock wave lithotripsy.	A*

For stones in the conduit, a trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy and flexible endoscopes. Trans-stomal manipulations in continent urinary diversion must be performed carefully to avoid disturbance of the continence mechanism [346].

Before considering any percutaneous approach in these cases, CT should be undertaken to assess the presence of an overlying bowel, which could make this approach unsafe [347], and if present, an open surgical approach should be considered.

3.4.5.2.3 Prevention

Recurrence risk is high in these patients [344]. Metabolic evaluation and close follow-up are necessary to obtain the risk parameters for effective long-term prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and hyperdiuresis or regular irrigation of continent reservoirs [348].

3.4.5.3 Management of stones in patients with neurogenic bladder

3.4.5.3.1 Aetiology, clinical presentation and diagnosis

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, pelvicaliectasis, VUR, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect [349]. The most common causes are urinary stasis and infection (Section 3.1.3). Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction both facilitate UTI. Although calculi can form at any level of the urinary tract, they occur more frequently in the bladder; especially if bladder augmentation has been performed [350, 351].

Diagnosis of stones may be difficult and delayed in the absence of clinical symptoms due to sensory impairment and vesicourethral dysfunction. Difficulties in self-catheterisation should lead to suspicion of bladder calculi. Imaging studies are needed (US, CT) to confirm the clinical diagnosis prior to surgical intervention.

3.4.5.3.2 Management

Management of calculi in patients with neurogenic bladder is similar to that described in Section 3.3.3. In MMC (myelomeningocele) patients, latex allergy is common, therefore, appropriate measures need to be taken regardless of the treatment [352]. Any surgery in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia. Bone deformities often complicate positioning on the operating table [353]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [348].

For efficient long-term stone prevention in patients with neurogenic bladder, correction of the metabolic disorder, appropriate infection control, and restoration of normal storing/voiding function of the bladder are needed.

Summary of evidence	LE
Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.	3

Recommendation	GR
Take appropriate measures regardless of the treatment provided since in myelomeningocele patients latex allergy is common.	B

3.4.5.4 Management of stones in transplanted kidneys

3.4.5.4.1 Aetiology

Transplant patients depend on their solitary kidney for renal function. Impairment causing urinary stasis/obstruction therefore requires immediate intervention or drainage of the transplanted kidney. Risk factors in these patients are multifold:

- immunosuppression increases the infection risk, resulting in recurrent UTIs;
- hyper filtration, excessively alkaline urine, renal tubular acidosis, and increased serum calcium caused by persistent tertiary hyperparathyroidism [354] are biochemical risk factors.

Stones in kidney allografts have an incidence of 0.2-1.7% [355-357].

Recommendation	LE	GR
Perform ultrasound or non-contrast-enhanced computed tomography to rule out calculi in patients with transplanted kidneys, unexplained fever, or unexplained failure to thrive (particularly in children) [358].	4	B

3.4.5.4.2 Management

Selecting the appropriate technique for stone removal in a transplanted kidney is difficult, although management principles are similar to those applied in other single renal units [359-362]. Additional factors such as transplant function, coagulative status, and anatomical obstacles due to the iliacal position of the organ, directly influence the surgical strategy.

For large or ureteral stones, careful percutaneous access and subsequent antegrade endoscopy are more favourable. The introduction of small flexible ureteroscopes and the holmium laser has made ureterorenoscopy a valid treatment option for transplant calculi. However, one must be aware of potential injury to adjacent organs [363-365]. Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [366-368].

Summary of evidence	LE
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.	
Shock wave lithotripsy for small calyceal stones is an option with minimal complication risk, but localisation of the stone can be challenging and stone-free rates are poor [369, 370].	4

Recommendations	GR
Offer patients with transplanted kidneys, any of the contemporary management options, including shock wave therapy, flexible ureteroscopy and percutaneous nephrolithotomy.	B
Complete metabolic evaluation after stone removal.	A*

*Upgraded following panel consensus.

3.4.5.4.3 Special problems in stone removal

Table 3.4.6: Special problems in stone removal

Calyceal diverticulum stones	<ul style="list-style-type: none"> Shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PNL) (if possible) or retrograde renal surgery (RIRS). Can also be removed using laparoscopic retroperitoneal surgery [371-375]. Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due to narrow calyceal neck.
Horseshoe kidneys	<ul style="list-style-type: none"> Can be treated in line with the options described above [376]. Passage of fragments after SWL might be poor. Acceptable SFRs can be achieved with flexible ureteroscopy [377].
Stones in pelvic kidneys	<ul style="list-style-type: none"> SWL, RIRS, PNL or laparoscopic surgery. In obese patients, the options are RIRS, PNL or open surgery.
Stones formed in a continent reservoir	<ul style="list-style-type: none"> See Section 3.4.4. Each stone must be considered and treated individually.
Patients with obstruction of the ureteropelvic junction	<ul style="list-style-type: none"> When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. Ureterorenoscopy together with endopyelotomy with holmium: yttrium-aluminium-garnet laser. Incision with an Acucise® balloon catheter might be considered, provided the stones can be prevented from falling into the pelvi-ureteral incision [378-381]. Open surgery with correction of the UPJ obstruction (pyeloplasty) and stone removal is a feasible option [382].

3.4.6 Management of urolithiasis in children

Rates of urolithiasis have increased in developed countries, and there has been a shift in the age group experiencing a first stone episode [10, 383, 384]. More than 1% of all urinary stones are seen in patients aged < 18 years. As a result of malnutrition and racial factors, paediatric urolithiasis remains an endemic disease in some areas (e.g., Turkey and the Far East); elsewhere, the rates are similar to those observed in developed countries [385-388].

For diagnostic procedures see Section 3.3.3.2, for acute decompression see Section 3.4.1.2.

3.4.6.1 Stone removal

Several factors must be considered when selecting treatment procedures for children. Compared to adults, children pass fragments more rapidly after SWL [52]. For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS. Stone composition should be taken into account when selecting the appropriate procedure for stone removal (cystine stones are more resistant to SWL).

Summary of evidence	LE
Spontaneous passage of a stone is more likely in children than in adults [62].	4

3.4.6.1.1 Medical expulsive therapy in children

Medical expulsive therapy has already been discussed in Section 3.4.3.1.2 but not addressing children. Although the use of α -blockers is very common in adults, there are limited data to demonstrate their safety and efficacy in children; however, tamsulosin seems to support stone passage [65, 389-393].

3.4.6.1.2 Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy remains the least-invasive procedure for stone management in children [394-399].

Stone-free-rates of 67-93% in short-term and 57-92% in long-term follow-up studies have been reported. In children, compared with adults, SWL can achieve more effective disintegration of large stones, together with swifter and uncomplicated discharge of large fragments [396, 400]. As in adults, the slow delivery rate of shock waves may improve the stone clearance rates [400]. Stones located in calices, as well as in abnormal kidneys, and large stones, are more difficult to disintegrate and clear. The likelihood of urinary obstruction is higher in such cases, and children should be followed closely for the prolonged risk of urinary tract obstruction. The retreatment rate is 13.9-53.9%, and the need for ancillary procedures and/or additional interventions is 7-33% [396, 398].

The need for general anaesthesia during SWL depends on patient age and the lithotripter used. General or dissociative anaesthesia is administered in most children aged < 10 years, to prevent patient and stone motion and the need for repositioning [396, 398]. With modern lithotripters, intravenous sedation or patient-controlled analgesia have been used in selected co-operative older children [401] (LE: 2b). There are concerns regarding the safety and potential biological effects of SWL on immature kidneys and surrounding organs in children. However, during short- and long-term follow-up, no irreversible functional or morphological side effects of high-energy shock waves have been demonstrated. In addition, when the potential deterioration of renal function is taken into account (although transient), restricting the number of shock waves and the energy used during each treatment session helps protect the kidneys [402-405].

If the stone burden requires a ureteral stent, alternative procedures should be considered. Ureteral stents are seldom needed following SWL of upper tract stones, ureteral pre-stenting decreases the SFR after initial treatment [394-396].

Summary of evidence	LE
In children, the indications for shock wave lithotripsy are similar to those in adults; however, children pass fragments more easily.	3
Children with renal stones of a diameter up to 20 mm (~300 mm ²) are ideal candidates for shock wave lithotripsy.	1b

3.4.6.1.3 Endourological procedures

Improvement in intracorporeal lithotripsy devices and development of smaller instruments facilitate PNL and URS in children.

3.4.6.1.3.1 Percutaneous nephrolithotomy

Pre-operative evaluation and indications for PNL in children are similar to those in adults. Provided appropriate size instruments and US guidance are used, age is not a limiting factor, and PNL can be performed safely by experienced operators, with less radiation exposure, even for large and complex stones [406-410]. Stone-free rates are between 68% and 100% after a single session, and increase with adjunctive measures, such as second-look PNL, SWL and URS [406].

As for adults, tubeless PNL is safe in children, in well-selected cases [411, 412].

Summary of evidence	LE
In children, the indications for percutaneous nephrolithotomy are similar to those in adults.	1a

Recommendation	GR
In children, perform percutaneous nephrolithotomy for the treatment of renal pelvic or calyceal stones with a diameter > 20 mm (~300 mm ²). For ureteral stones, ureterorenoscopy may be an alternative, in case shockwave lithotripsy does not look promising.	

3.4.6.1.3.2 Ureteroscopy

Although SWL is still the first-line treatment for most ureteral stones, it is unlikely to be successful for stones > 10 mm in diameter, or for impacted stones, calcium oxalate monohydrate or cystine stones, or stones in children with unfavourable anatomy and in whom localisation is difficult [413, 414].

If SWL is not promising, ureteroscopy can be used. With the clinical introduction of smaller-calibre instruments, this modality has become the treatment of choice for medium and larger distal ureteric stones in children [413-417].

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all safe and effective (Section 3.4.3.1.4.1.2) [418, 419].

Recommendation	LE	GR
For intracorporeal lithotripsy, use the same devices as in adults (holmium: yttrium-aluminium-garnet laser, pneumatic- and ultrasound lithotripters).	3	C

Flexible URS

Despite concerns about the potential risks and complications related to endoscopic surgery of children's delicate ureter and collecting system, with the development of smaller size endoscopes, flexible ureteroscopy (RIRS) has become an efficacious treatment modality for renal and ureteral stones [413, 419-421] and might be a particularly effective treatment option for lower calyx stones in the presence of unfavourable factors for SWL.

Similar to adults, routine stenting is not necessary before URS. However, leaving a ureteral stent for the subsequent session must be considered in case of failure of ureteroscopy. Pre-stenting facilitates URS, increases SFR and decreases complication rates [422].

For large and complex kidney stones PNL has a higher SFR compared to RIRS, but RIRS is associated with less radiation exposure, lower complication rates and a shorter hospital stay [423]. The experience of the surgical team is of the utmost importance for the success of both endourological techniques.

3.4.6.1.3.3 Open or laparoscopic surgery

Most stones in children can be managed by SWL and endoscopic techniques. Therefore, the rate of open procedures has dropped significantly [424-426]. Indications for surgery include: failure of primary therapy for stone removal; very young children with complex stones; congenital obstruction that requires simultaneous surgical correction; severe orthopaedic deformities that limit positioning for endoscopic procedures; and abnormal kidney position [394, 395, 407]. Open surgery can be replaced by laparoscopic procedures in experienced hands [425, 426].

3.4.6.1.3.4 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. In radiolucent stones oral chemolysis may be considered as an alternative to SWL [427]. In the case of obstructive pathology in association with the established metabolic abnormalities, treatment should not be delayed. Children are in the high-risk group for stone recurrence [65, 428] (Chapter 4).

4. FOLLOW UP: METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

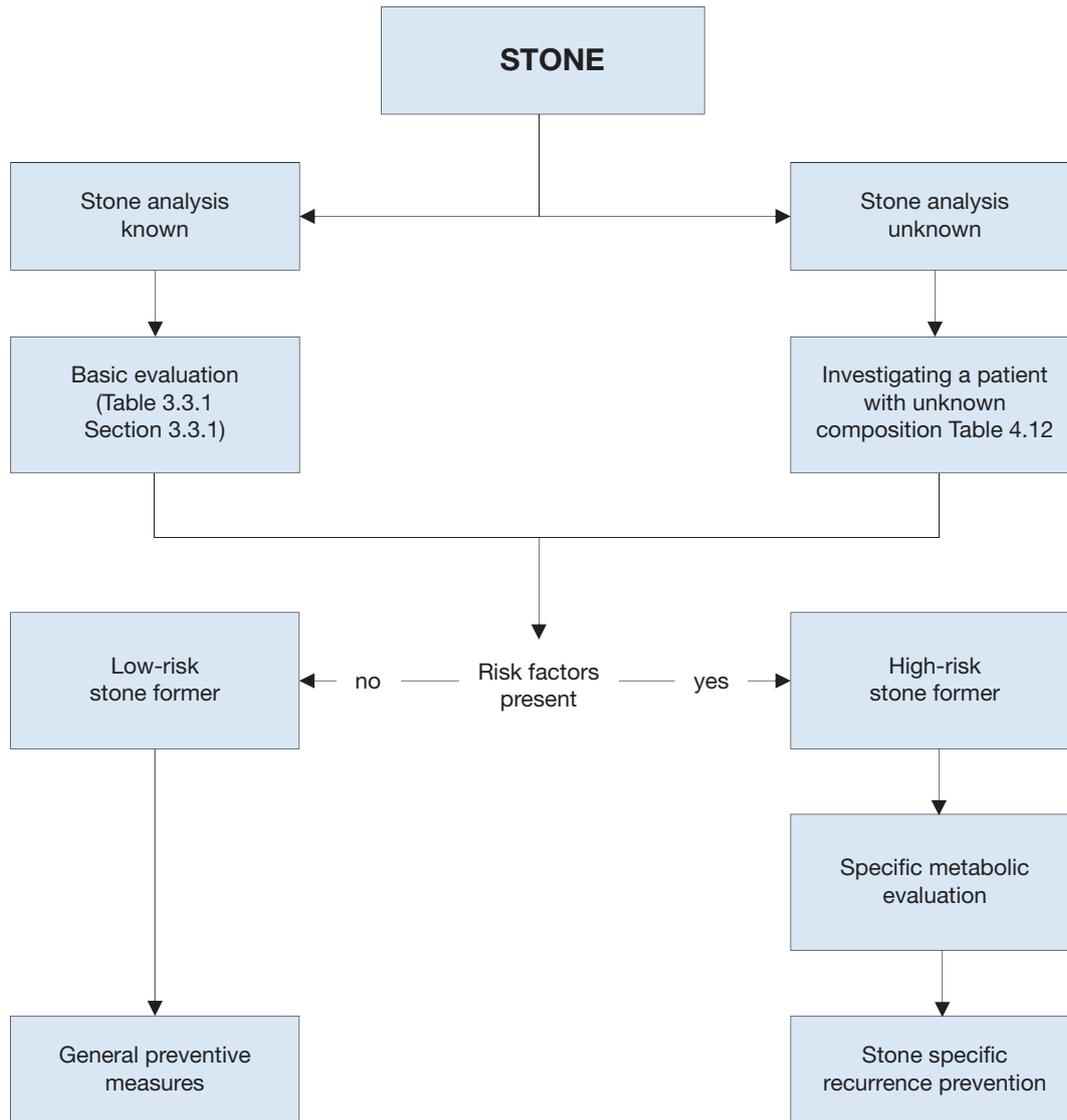
4.1.1 Evaluation of patient risk

After stone passage, every patient should be assigned to a low- or high-risk group for stone formation (Figure 4.1).

For correct classification, two items are mandatory:

- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis (Section 3.3.2).

Figure 4.1 Assignment of patients to low- or high-risk groups for stone formation



Only high-risk stone formers require specific metabolic evaluation. Stone type is the deciding factor for further diagnostic tests. The different stone types include:

- calcium oxalate;
- calcium phosphate;
- uric acid;
- ammonium urate;
- struvite (and infection stones);
- cystine;
- xanthine;
- 2,8-Dihydroxyadenine;
- drug stones;
- stones of unknown composition.

4.1.2 Urine sampling

Specific metabolic evaluation requires collection of two consecutive 24-hour urine samples [429, 430]. The collecting bottles should be prepared with 5% thymol in isopropanol or stored at $< 8^{\circ}\text{C}$ during collection to prevent the risk of spontaneous crystallisation in the urine [431, 432]. Pre-analytical errors can be minimised by carrying out urinalysis immediately after collection. Alternatively, boric acid (10 g powder per urine container) can also be used. The collecting method should be chosen in close cooperation with the particular laboratory. Urine pH should be assessed during collection of freshly voided urine four times daily [16, 431] using sensitive pH-dipsticks or a pH-meter.

Spot urine samples are an alternative method of sampling, particularly when 24-hours urine collection is difficult, for example, in non-toilet trained children [433]. Spot urine studies normally link the excretion rates to creatinine [433], but these are of limited use because the results may vary with collection time and patients' sex, body weight and age.

4.1.3 **Timing of specific metabolic work-up**

For the initial specific metabolic work-up, the patient should stay on a self-determined diet under normal daily conditions and should ideally be stone free for at least twenty days [434].

Follow-up studies are necessary in patients taking medication for recurrence prevention [435]. The first follow-up 24-hour urine measurement is suggested eight-twelve weeks after starting pharmacological prevention of stone recurrence. This enables drug dosage to be adjusted if urinary risk factors have not normalised, with further 24-hour urine measurements if necessary. Once urinary parameters have been normalised, it is sufficient to perform 24-hour urine evaluation every twelve months. The panel realise that on this issue there is only very limited published evidence. The Urolithiasis Guidelines Panel aim to set up a SR on the ideal timing of the 24-hour urine collection.

4.1.4 **Reference ranges of laboratory values**

Tables 4.1 - 4.4 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.

Table 4.1: Normal laboratory values for blood parameters in adults [436]

Blood parameter	Reference range	
Creatinine	20-100 $\mu\text{mol/L}$	
Sodium	135-145 mmol/L	
Potassium	3.5-5.5 mmol/L	
Calcium	2.0-2.5 mmol/L (total calcium)	
	1.12-1.32 mmol/L (ionised calcium)	
Uric acid	119-380 $\mu\text{mol/L}$	
Chloride	98-112 mmol/L	
Phosphate	0.81-1.29 mmol/L	
Blood gas analysis	pH	7.35-7.45
	pO ₂	80-90 mmHg
	pCO ₂	35-45 mmHg
	HCO ₃	22-26 mmol/L
	BE	± 2 mmol/L

BE = base excess (loss of buffer base to neutralise acid); HCO = bicarbonate; PCO = partial pressure of carbon dioxide; PO = partial pressure of oxygen.

4.1.5 **Risk indices and additional diagnostic tools**

Several risk indices have been developed to describe the crystallisation risk for calcium oxalate or calcium phosphate in urine [437-440]. However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing.

Table 4.2: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8 (suspicious of renal tubular acidosis)
	Constantly > 7.0 (suspicious of infection)
	Constantly ≤ 5.8 (suspicious of acidic arrest)
Specific weight	> 1.010
Creatinine	7-13 mmol/day females
	13-18 mmol/day males
Calcium	> 5.0 mmol/day (see Fig. 4.2)
	≥ 8.0 mmol/day (see Fig. 4.2)
Oxalate	> 0.5 mmol/day (suspicious of enteric hyperoxaluria)
	≥ 1.0 mmol/day (suspicious of primary hyperoxaluria)
Uric acid	> 4.0 mmol/day (women), 5 mmol/day (men)
Citrate	< 2.5 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in adults [441]

Parameter/Patient age	Ratio of solute to creatinine	Units
Calcium	mol/mol	mg/mg
< 12 months	< 2.0	0.81
1-3 years	< 1.5	0.53
1-5 years	< 1.1	0.39
5-7 years	< 0.8	0.28
> 7 years	< 0.6	0.21
Oxalate	mol/mol	mg/g
0-6 months	< 325-360	288-260
7-24 months	< 132-174	110-139
2-5 years	< 98-101	80
5-14 years	< 70-82	60-65
> 16 years	< 40	32
Citrate	mol/mol	g/g
0-5 years	> 0.25	0.42
> 5 years	> 0.15	0.25
Magnesium	mol/mol	g/g
	> 0.63	> 0.13
Uric acid	< 0.56 mg/dl (33 imol/L) per GFR (ratio x plasma creatinine)	
> 2 years		

Table 4.4: Solute excretion in 24-hour urine samples in children [441]**

Calcium/24 hour	Citrate/24 hour		Cystine/24 hour		Oxalate/24 hour		Urate/24 hour	
	Boys	Girls	< 10 years	> 10 years	All age groups	< 1 year	1-5 years	> 5 years
< 0.1 mmol/kg/24 h	> 1.9 mmol/1.73 m ² /24 h	> 1.6 mmol/1.73 m ² /24 h	< 55 μmol/1.73 m ² /24 h	< 200 μmol/1.73 m ² /24 h	< 0.5 mmol/1.73 m ² /24 h	< 70 μmol/kg/24 h	< 65 μmol/kg/24 h	< 55 μmol/kg/24 h
< 4 mg/kg/24 h	> 365 mg/1.73 m ² /24 h	> 310 mg/1.73 m ² /24 h	< 13 mg/1.73 m ² /24 h	< 48 mg/1.73 m ² /24 h	< 45 mg/1.73 m ² /24 h	< 13 mg/kg/24 h	< 11 mg/kg/24 h	< 9.3 mg/kg/24 h

**24 h urine parameters are diet and gender dependent and may vary geographically.

4.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 4.5. The main focus of these is normalisation of dietary habits and lifestyle risks. Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment based on stone analysis.

Table 4.5: General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day
	Circadian drinking
	Neutral pH beverages
	Diuresis: 2.0-2.5 L/day
	Specific weight of urine: < 1010
Nutritional advice for a balanced diet	Balanced diet*
	Rich in vegetables and fibre
	Normal calcium content: 1-1.2 g/day
	Limited NaCl content: 4-5 g/day
	Limited animal protein content: 0.8-1.0 g/kg/day
Lifestyle advice to normalise general risk factors	BMI: retain a normal BMI level
	Adequate physical activity
	Balancing of excessive fluid loss

Caution: The protein need is age dependent; therefore, protein restriction in childhood should be handled carefully.

** Avoid excessive consumption of vitamin supplements.*

4.2.1 Fluid intake

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated [442-444]. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [445]. If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased [446, 447]. One large fair-quality RCT randomly assigned men with more than one past renal stone of any type and soft drink consumption of at least 160 mL/day to reduced soft drink intake or no treatment. Although the intervention significantly reduced the risk for symptomatic recurrent stones (RR: 0.83; CI: 0.71-0.98), the level of evidence for this outcome was low because results were from only one trial [444, 448].

4.2.2 Diet

A common sense approach to diet should be taken, that is, a mixed balanced diet with contributions from all food groups, without any excesses [444, 449, 450].

Fruits, vegetables and fibres: fruit and vegetable intake should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable [451-454]. The alkaline content of a vegetarian diet also increases urinary pH.

Oxalate: excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load [445], particularly in patients who have high oxalate excretion.

Vitamin C: although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial [455]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: should not be taken in excess [456, 457] and limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria.

Calcium intake: should not be restricted unless there are strong reasons due to the inverse relationship between dietary calcium and stone formation [452, 458]. The daily requirement for calcium is 1,000 to 1,200 mg [16]. Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate [444, 457, 459]. Older adults, who do not have a history of renal stones but who take calcium supplements should ensure adequate fluid intake since it may prevent increases in urine calcium concentration, and thereby reduce or eliminate any increased risk of renal stones formation associated with calcium supplement use [460].

Sodium: the daily sodium (NaCl) intake should not exceed 3-5 g [16]. High intake adversely affects urine composition:

- calcium excretion is increased by reduced tubular reabsorption;
- urinary citrate is reduced due to loss of bicarbonate;
- increased risk of sodium urate crystal formation.

Calcium stone formation can be reduced by restricting sodium and animal protein [456, 457]. A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women [458, 461]. There have been no prospective clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Urate: intake of purine-rich food should be restricted in patients with hyperuricosuric calcium oxalate [462, 463] and uric acid stones. Intake should not exceed 500 mg/day [16].

4.2.3 **Lifestyle**

Lifestyle factors may influence the risk of stone formation, for example, obesity [464] and arterial hypertension [465, 466].

4.2.4 **Recommendations for recurrence prevention**

Recommendations	LE	GR
Advise patients that a generous fluid intake is to be maintained, allowing for a 24-hour urine volume > 2.5 L.	1b	A
Advise patients with a small urine volume to increase their fluid intake.	1b	a

4.3 **Stone-specific metabolic evaluation and pharmacological recurrence prevention**

4.3.1 **Introduction**

Pharmacological treatment is necessary in patients at high risk for recurrent stone formation. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance. Table 4.6 highlights the most important characteristics of commonly used medication.

Table 4.6: Pharmacological substances used for stone prevention - characteristics, specifics and dosage

Agent	Rationale	Dose	Specifics and side effects	Stone type	Ref
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	5-12 g/d (14-36 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid Cystine	[49, 444, 467-474]
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria Renal insufficiency demands dose correction	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine	[475-479]
Calcium	Enteric hyperoxaluria	1000 mg/d	Intake 30 min before meals	Calcium oxalate	[457-459]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine	[480, 481]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate Uric acid	[482, 483]
L-Methionine	Acidification	600-1500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[49, 484, 485]
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia.	Calcium oxalate	[486, 487] low evidence
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid, Cystine	[488]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	[489]
Thiazide (Hydrochlorothiazide)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for agent-induced hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia.	Calcium oxalate Calcium phosphate	[49, 486, 490-498]
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2000 mg/d	Risk for tachyphylaxis and proteinuria.	Cystine	[499-502]

4.4 Calcium oxalate stones

The criteria for identification of calcium oxalate stone formers with high recurrence risk are listed in Section 3.1.2.

4.4.1 *Diagnosis*

Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), uric acid, and parathyroid hormone (PTH) (and vitamin D) in the case of increased calcium levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight, calcium, oxalate, uric acid, citrate, sodium and magnesium.

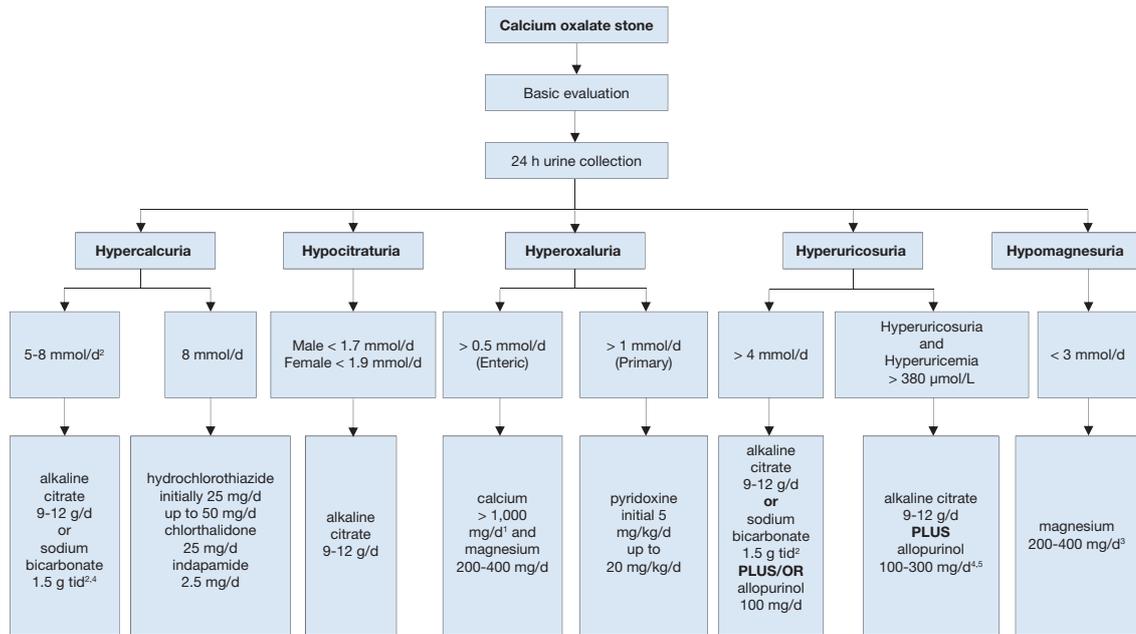
4.4.2 *Interpretation of results and aetiology*

The diagnostic and therapeutic algorithm for calcium oxalate stones is shown in Figure 4.2 [49, 444, 468-470, 475-477, 482, 486-488, 490-497, 503-507].

The most common metabolic abnormalities associated with calcium stone formation are hypercalciuria, which affects 30-60% of adult stone formers, and hyperoxaluria (26-67%), followed by hyperuricosuria (15-46%), hypomagnesiuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ based on ethnicity [503].

- Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- “Acidic arrest” (urine pH constantly < 5.8) may promote co-crystallisation of uric acid and calcium oxalate.
- Similarly, increased uric acid excretion (> 4 mmol/day in adults or > 12 mg/kg/day in children) can act as a promoter.
- Urine pH levels constantly > 5.8 in the day profile indicate renal tubular acidosis (RTA), provided UTI has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (Section 4.6.5).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (hyperparathyroidism, granulomatous diseases, vitamin D excess, or malignancy).
- Hypocitraturia (male < 1.7 mmol/d, female < 1.9 mmol/d) may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Oxalate excretion > 0.5 mmol/day in adults (> 0.37 mmol/1.73 m²/day in children) confirms hyperoxaluria.
 - o primary hyperoxaluria (oxalate excretion mostly > 1 mmol/day), appears in three genetically determined forms;
 - o secondary hyperoxaluria (oxalate excretion > 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
 - o mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesiuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea).

Figure 4.2: Diagnostic and therapeutic algorithm for calcium oxalate stones



¹ Be aware of excess calcium excretion.

² tid = three times/day (24h).

³ No magnesium therapy for patients with renal insufficiency.

⁴ There is no evidence that combination therapy (thiazide + citrate) (thiazide + allopurinol) is superior to thiazide therapy alone [490, 497].

⁵ Febuxostat 80 mg/d.

4.4.3 Specific treatment

General preventive measures are recommended for fluid intake and diet. Hyperoxaluric stone formers should consume foods with low oxalate content, whereas hyperuricosuric stone formers benefit from daily dietary reduction of purine. Figure 4.2 summarises the diagnostic algorithm and the pharmacological treatment of calcium oxalate stones [49, 444, 468-470, 475-477, 482, 486-488, 490-497, 503-507]. There is only low level evidence on the efficacy of preventing stone recurrence through pre-treatment stone composition and biochemistry measures, or on-treatment biochemistry measures [444].

4.4.4 Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition (based on 24-hour urine samples)

Urinary risk factor	Suggested treatment	LE	GR
Hypercalcaemia	Thiazide + potassium citrate	1a	A
Hyperoxaluria	Oxalate restriction	2b	A
Enteric hyperoxaluria	Potassium citrate	3-4	C
	Calcium supplement	2	B
	Diet reduced in fat and oxalate	3	B
Hypocitraturia	Potassium citrate	1b	A
Hypocitraturia	Sodium bicarbonate if intolerant to potassium citrate	1b	A
Hyperuricosuria	Allopurinol	1a	A
	Febuxostat	1b	A
High sodium excretion	Restricted intake of salt	1b	A
Small urine volume	Increased fluid intake	1b	A
Urea level indicating a high intake of animal protein	Avoid excessive intake of animal protein	1b	A
No abnormality identified	High fluid intake	2b	B

4.5 Calcium phosphate stones

Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is provided in Section 3.1.2.

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite. Carbonate apatite crystallisation occurs at a pH > 6.8 and may be associated with infection.

Brushite crystallises at an optimum pH of 6.5-6.8, at high urinary concentrations of calcium (> 8 mmol/day) and phosphate (> 35 mmol/day). Its occurrence is not related to UTI.

Possible causes of calcium phosphate stones include HPT, RTA and UTI; each of which requires different therapy.

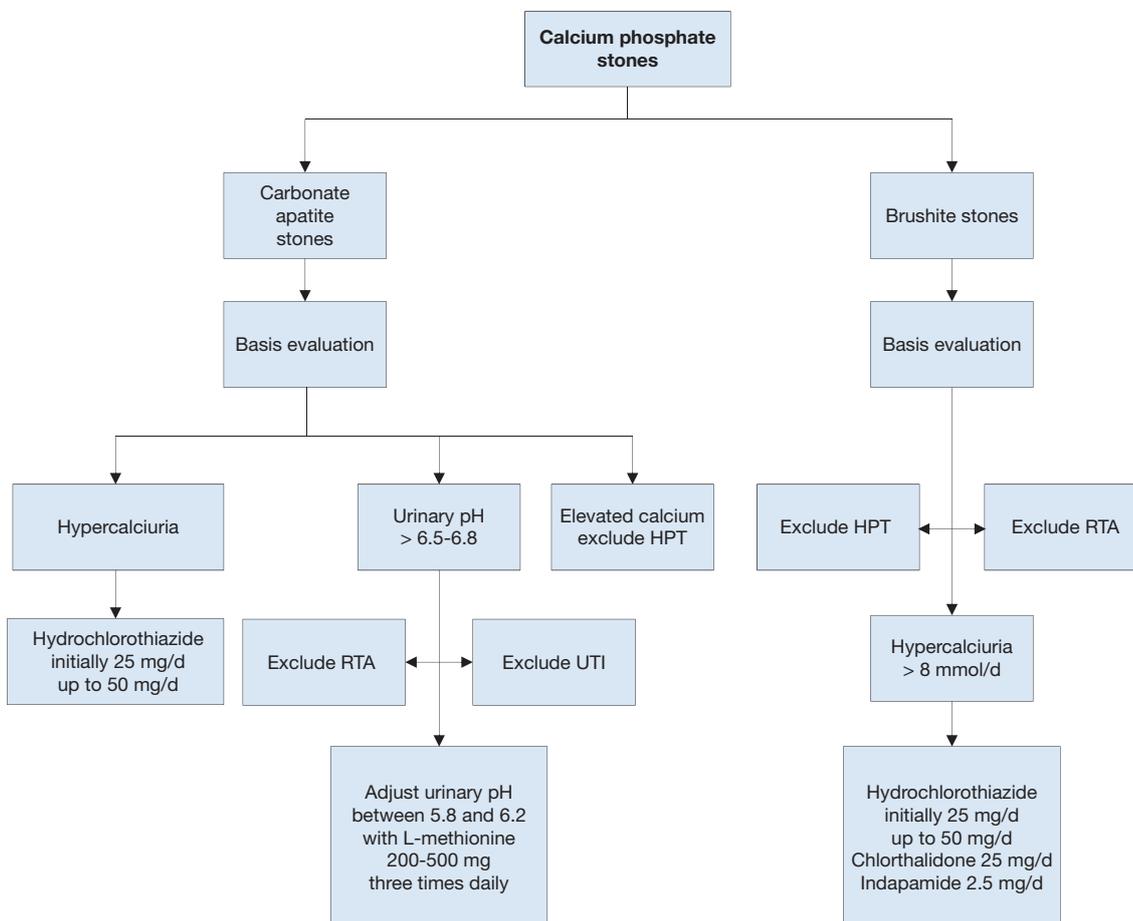
4.5.1 Diagnosis

Diagnosis requires blood analysis for: creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), and PTH (in the case of increased calcium levels). Urinalysis includes measurement of: volume, urine pH profile, specific weight, calcium, phosphate and citrate.

4.5.2 Interpretation of results and aetiology

General preventive measures are recommended for fluid intake and diet. The diagnostic and therapeutic algorithm for calcium phosphate stones is shown in Figure 4.3.

Figure 4.3: Diagnostic and therapeutic algorithm for calcium phosphate stones



HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection.

4.5.3 Pharmacological therapy [49, 444, 490, 491, 495, 507]

Hyperparathyroidism and RTA are common causes of calcium phosphate stone formation. Although most patients with primary HPT require surgery, RTA can be corrected pharmacologically. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides. If urine pH remains constantly > 6.2, urinary acidification with L-methionine may be beneficial; however, it is not commonly used and needs monitoring for systemic acidosis development. For

infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

4.5.4 Recommendations for the treatment of calcium phosphate stones

Urinary risk factor and suggested treatment	LE	GR
Prescribe thiazide in case of hypercalciuria.	1a	A
Advise patients to acidify their urine in case of inadequate urine pH.	3-4	C
Prescribe antibiotics in case of a urinary tract infection.	3-4	C

4.6 Disorders and diseases related to calcium stones

4.6.1 Hyperparathyroidism [508-511]

Primary HPT is responsible for an estimated 5% of all calcium stone formation. Renal stones occur in approximately 20% of patients with primary HPT. Elevated levels of PTH significantly increase calcium turnover, leading to hypercalcaemia and hypercalciuria. Serum calcium may be mildly elevated and serum PTH may be within the upper normal limits, therefore, repeated measurements may be needed; preferably with the patient fasting. Stones of HPT patients may contain both calcium oxalate and calcium phosphate.

If HPT is suspected, neck exploration should be performed to confirm the diagnosis. Primary HPT can only be cured by surgery.

4.6.2 Granulomatous diseases [511]

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcaemia and hypercalciuria secondary to increased calcitriol production. The latter is independent of PTH control, leading to increased calcium absorption in the gastrointestinal tract and suppression of PTH. Treatment focusses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine or ketoconazole. Treatment should be reserved for the specialist.

4.6.3 Primary hyperoxaluria [489]

Patients with primary hyperoxaluria (PH) should be referred to specialised centres, as successful management requires an experienced interdisciplinary team. The main therapeutic aim is to reduce endogenous oxalate production, which is increased in patients with PH. In approximately one-third of patients with PH type I, pyridoxine therapy normalises or significantly reduces urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting fluid intake to 3.5-4.0 L/day in adults (children 1.5 L/m² body surface area) and following a circadian drinking regimen.

Therapeutic options for preventing calcium oxalate crystallisation include hyperdiuresis, alkaline citrates and magnesium. However, in end-stage renal failure, PH requires simultaneous liver-kidney transplantation.

Treatment regimens are:

- pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
- alkaline citrate: 9-12 g/day in adults, 0.1-0.15 meq/kg/day in children;
- magnesium: 200-400 mg/day (no magnesium in the case of renal insufficiency).

Urinary risk factor and suggested management of primary hyperoxaluria	LE	GR
Refer patients diagnosed with primary hyperoxaluria to a specialised centre where multidisciplinary care can be provided.		
Prescribe pyridoxine for primary hyperoxaluria.	3	B

4.6.4 Enteric hyperoxaluria [459, 512]

Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation, and is seen after intestinal resection and malabsorptive bariatric surgery and in Crohn's disease and pancreas insufficiency. In addition to hyperoxaluria, these patients usually present with hypocitraturia due to loss of alkali. Urine pH is usually low, as are urinary calcium and urine volume. All these abnormalities contribute to high levels of supersaturation with calcium oxalate, crystalluria, and stone formation.

Specific preventive measures are:

- restricted intake of oxalate-rich foods;

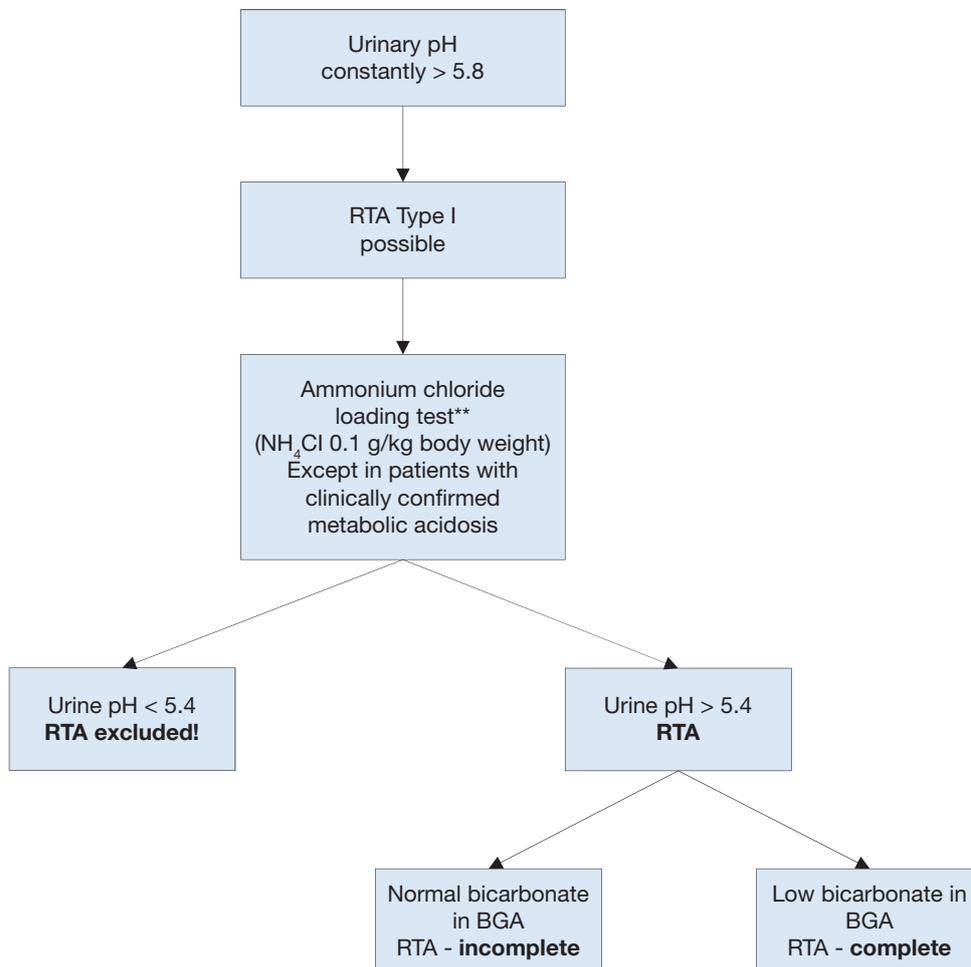
- restricted fat intake;
- calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine [459, 512];
- sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
- alkaline citrates to raise urinary pH and citrate.

Urinary risk factor and suggested management of enteric hyperoxaluria	LE	GR
Prescribe potassium citrate.	4	C
Advise patients to take a calcium supplement.	2	B
Advise patients to follow a diet with a low fat and oxalate content.	3	B

4.6.5 Renal tubular acidosis [513, 514]

Renal tubular acidosis is caused by severe impairment of proton or bicarbonate handling along the nephron. Kidney stone formation most probably occurs in patients with distal RTA type I. Figure 4.4 outlines the diagnosis of RTA. Table 4.7 shows acquired and inherited causes of RTA.

Figure 4.4: Diagnosis of renal tubular acidosis



** An alternative Ammonium Chloride loading test using NH_4Cl load with 0.05 g/kg body weight over three days might provide similar results and may be better tolerated by the patient. A second alternative in these cases could be the furosemide acidification test.

Renal tubular acidosis can be acquired or inherited. Reasons for acquired RTA can be obstructive uropathy, recurrent pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, idiopathic hypercalcaemia, and primary parathyroidism; it may also be drug-induced (e.g. zonisamide). Table 4.7 shows the inherited causes of RTA.

Table 4.7: Inherited causes of renal tubular acidosis

Type - inheritance	Gene/gene product/function	Phenotype
Autosomal dominant	SLC4A1/AE1/Cl-bicarbonate exchanger	Hypercalciuria, hypokalaemia, osteomalacia
Autosomal recessive with hearing loss	ATP6V1B1/B1 subunit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets
Autosomal recessive	ATP6V0A4/A4 subunit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets

The main therapeutic aim of RTA treatment is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is key to normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 4.8). The alkali load reduces tubular reabsorption of citrate, which in turn normalises citrate excretion and simultaneously reduces calcium turnover. Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 2.0 mmol/L) in complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

Table 4.8: Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Rationale for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide, - in adults: 25 mg/day initially, up to 50 mg/day - in children: 0.5-1 mg/kg/day Alternatives in adults: Chlorthalidone 25 mg/d Indapamide 2.5 mg/d
Inadequate urine pH	Intracellular acidosis in nephron	Alkaline citrate, 9-12 g/day divided in three doses OR Sodium bicarbonate, 1.5 g, three times daily

Urinary risk factor and suggested management of renal tubular acidosis	LE	GR
Prescribe potassium citrate for distal renal tubular acidosis.	2b	B
Prescribe thiazide + potassium citrate for hypercalciuria.	1a	A

4.6.6 **Nephrocalcinosis** [441]

Nephrocalcinosis (NC) refers to increased crystal deposition within the renal cortex or medulla, and occurs alone or in combination with renal stones. There are various metabolic causes. The main risk factors are: HPT, PH, RTA, vitamin D metabolic disorders, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease, Bartter's syndrome and Medullary sponge kidney. The many causes of NC means there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, while minimising the biochemical risk factors.

4.6.6.1 *Diagnosis*

Diagnosis requires the following blood analysis: PTH (in the case of increased calcium levels), vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride, and blood gas analysis. Urinalysis should investigate: urine pH profile (minimum four times daily), daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium and citrate.

4.7 **Uric acid and ammonium urate stones**

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence [16]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [515]. They are associated with hyperuricosuria or low urinary pH. Hyperuricosuria may be a result of dietary excess, endogenous

overproduction (enzyme defects), myeloproliferative disorders, tumour lysis syndrome, drugs, gout or catabolism [516]. Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance or gout), increased endogenous acid production (insulin resistance, metabolic syndrome, or exercise-induced lactic acidosis), increased acid intake (high animal protein intake), or increased base loss (diarrhoea) [516].

Ammonium urate stones are extremely rare, comprising < 1% of all types of urinary stones. They are associated with UTI, malabsorption (inflammatory bowel disease and ileostomy diversion or laxative abuse), potassium deficiency, hypokalaemia and malnutrition.

Suggestions on uric acid and ammonium urate nephrolithiasis are based on level 3 and 4 evidence.

4.7.1 **Diagnosis**

Figure 4.5 shows the diagnostic and therapeutic algorithm for uric acid and ammonium urate stones. Blood analysis requires measurement of creatinine, potassium and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level. Urine culture is needed in the case of ammonium urate stones.

4.7.2 **Interpretation of results**

Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (urine pH constantly < 5.8) promotes uric acid crystallisation.

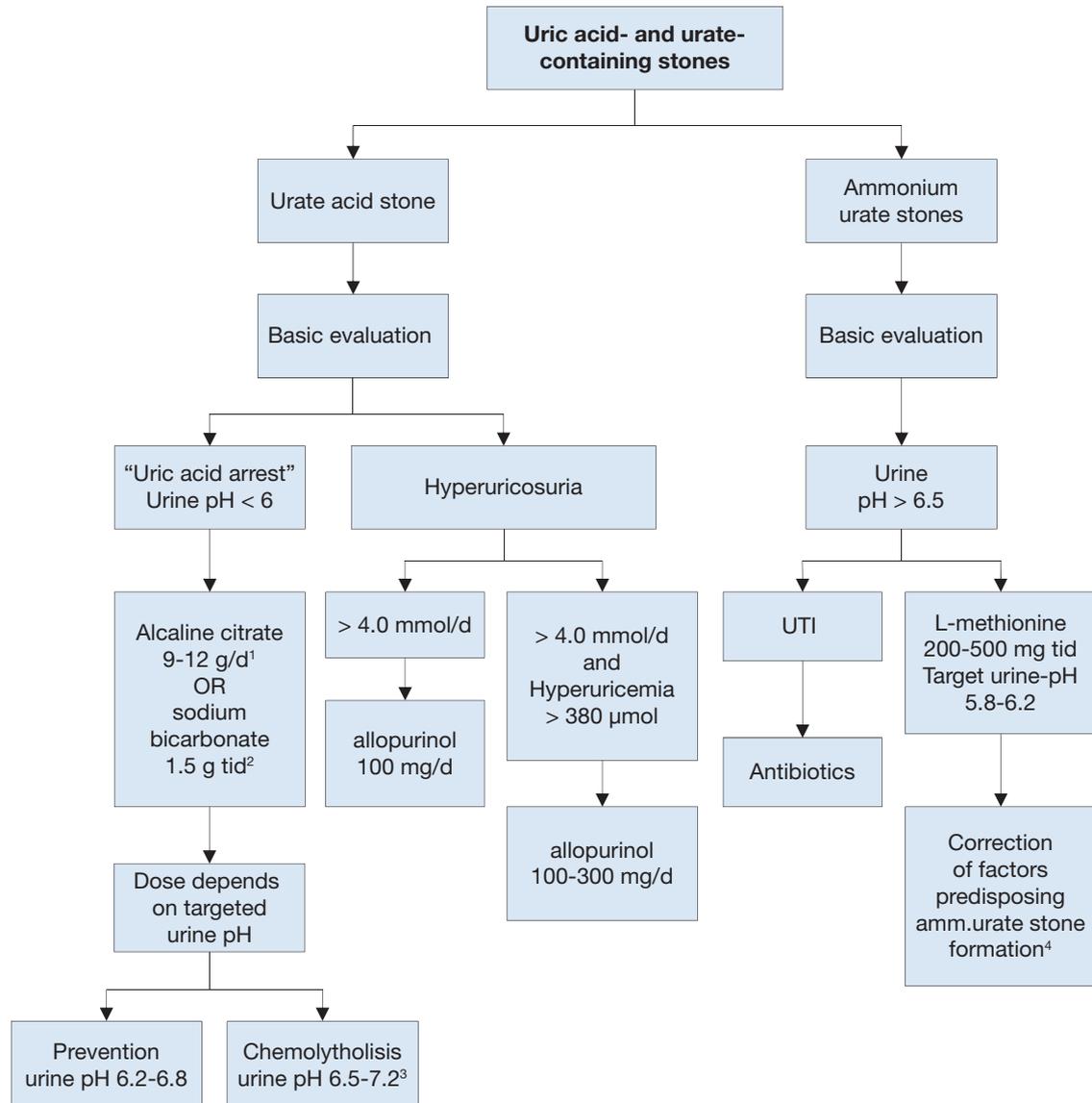
Hyperuricosuria is defined as uric acid excretion > 4 mmol/day in adults or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation.

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by: urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and occasional absence of hyperuricosuria in patients with pure uric acid stones [517, 518]. Ammonium urate crystals form in urine at pH > 6.5, at high uric acid concentration when ammonium is present to serve as a cation [519-521].

4.7.3 **Specific treatment**

General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction in their daily diet. Figure 4.5 describes pharmacological treatment [16, 433, 515-527]. For uric acid stones, allopurinol may change the stone composition distribution in patients with gout to a pattern similar to that in stone formers without gout [528].

Figure 4.5: Diagnostic and therapeutic algorithm for uric acid- and ammonium urate stones



¹ d: day.

² tid: three times a day.

³ A higher pH may lead to calcium phosphate stone formation.

⁴ In patients with high uric acid excretion, allopurinol may be helpful.

4.8 Struvite and infection stones

All infection-stone formers are deemed at high risk of recurrence. Struvite stones represent 2-15% of the stones sent for analysis. Stones that contain struvite may originate *de novo* or grow on pre-existing stones, which are infected with urea-splitting bacteria [529]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [530].

4.8.1 Diagnosis

Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture.

Interpretation

Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate. Urine culture typically provides evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine (Table 4.10). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2 [531, 532]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [533, 534].

4.8.2 **Specific treatment**

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [530], short- or long-term antibiotic treatment [535], urinary acidification using methionine [484] or ammonium chloride [536], and advice to restrict intake of urease [537, 538]. For severe infections, acetohydroxamic acid may be an option [537, 538] (Figure 4.6); however, it is not licensed/available in all European countries.

4.8.3 **Recommendations for therapeutic measures of infection stones**

Recommendations	LE	GR
Surgically remove the stone material as completely as possible.	3-4	A*
Prescribe a short-term antibiotic course.	3	B
Prescribe a long-term antibiotic course in case of recurrent infections.	3	B
Prescribe ammonium chloride, 1 g, two or three times daily to ensure urinary acidification.	3	B
Prescribe methionine, 200-500 mg, one-three times daily, as an alternative, to ensure urinary acidification.	3	B
Consider prescription of urease inhibitors in case of severe infection (if licensed).	1b	A

*Upgraded following panel consensus.

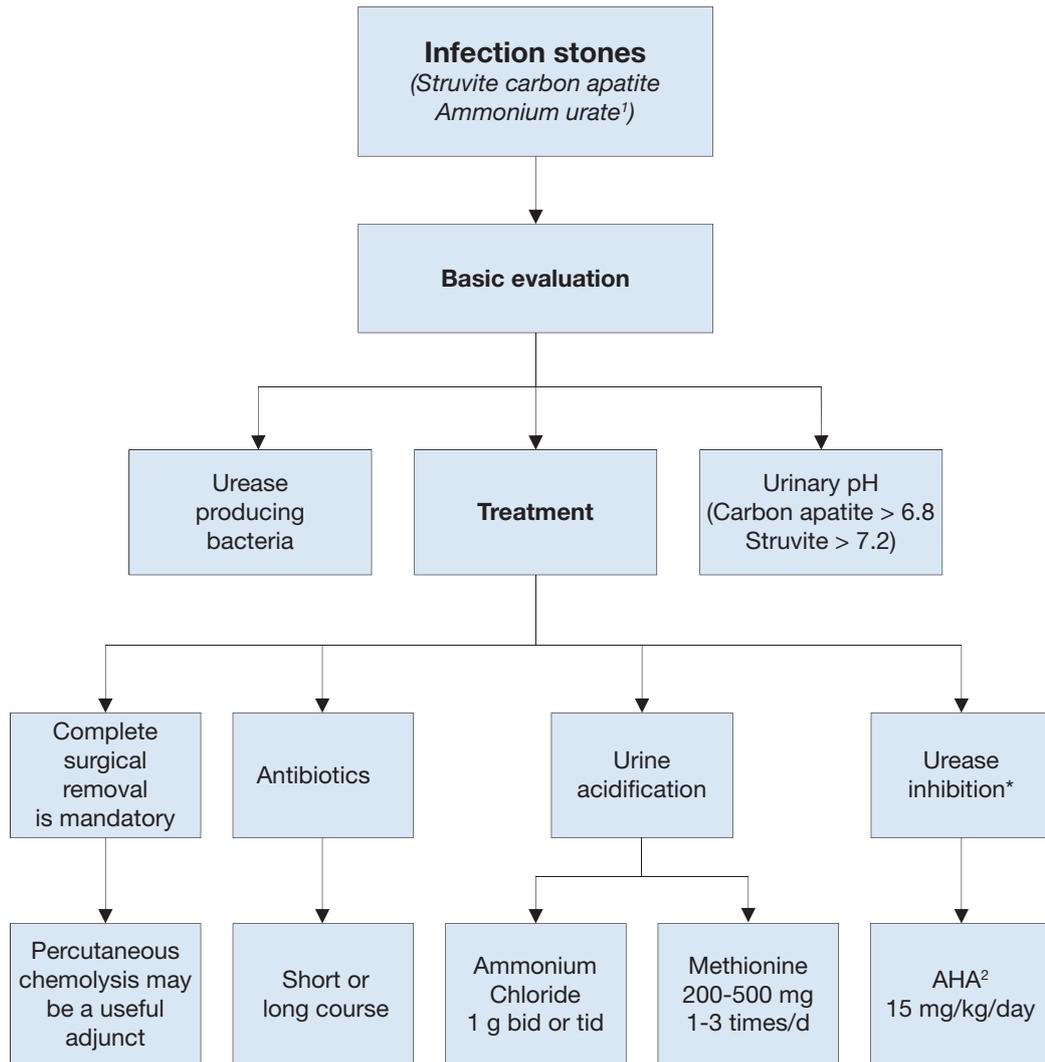
Table 4.9: Factors predisposing to struvite stone formation

Neurogenic bladder
Spinal cord injury/paralysis
Continent urinary diversion
Ileal conduit
Foreign body
Stone disease
Indwelling urinary catheter
Urethral stricture
Benign prostatic hyperplasia
Bladder diverticulum
Cystocele
Calyceal diverticulum
UPJ obstruction

Table 4.10: Most important species of urease-producing bacteria

Obligate urease-producing bacteria (> 98%)
<ul style="list-style-type: none"> • <i>Proteus spp.</i> • <i>Providencia rettgeri</i> • <i>Morganella morganii</i> • <i>Corynebacterium urealyticum</i> • <i>Ureaplasma urealyticum</i>
Facultative urease-producing bacteria
<ul style="list-style-type: none"> • <i>Enterobacter gergoviae</i> • <i>Klebsiella spp.</i> • <i>Providencia stuartii</i> • <i>Serratia marcescens</i> • <i>Staphylococcus spp.</i>
CAUTION: 0-5% of <i>Escherichia coli</i> , <i>Enterococcus spp.</i> and <i>Pseudomonas aeruginosa</i> strains may produce urease.

Figure 4.6: Diagnostic and therapeutic algorithm for infection stones



¹ Discussed with uric acid stones,

² Acetohydroxamic acid

* When nationally available.

bid = twice a day; tid = three times a day.

4.9 Cystine stones

Cystine stones account for 1-2% of all urinary stones in adults and 6-8% of the stones reported in paediatric studies [26, 539]. All cystine stone formers are deemed at high risk of recurrence.

4.9.1 Diagnosis

Blood analysis includes measurement of creatinine, and urinalysis includes measurement of urine volume, pH profile, specific weight, and cystine.

Interpretation

- Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range.
- Cystine solubility depends strongly on urine pH: at pH 6.0, the limit of solubility is 1.33 mmol/L.
- Routine analysis of cystine is not suitable for therapeutic monitoring.
- Regardless of phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [540].
- There is no role for genotyping patients in the routine management of cystinuria [541, 542].
- Reductive therapy targets the disulphide binding in the cysteine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only high-performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed by therapy.
- Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20-25% of urine specimens from patients with cystinuria [543].

- The cyanide nitroprusside colorimetric qualitative test detects the presence of cystine at a threshold concentration of 75 mg/L, with a sensitivity of 72% and specificity of 95%. False-positive results in patients with Fanconi's syndrome, homocystinuria, or those taking various drugs, including Infection stones
- Quantitative 24-hour urinary cystine excretion confirms the diagnosis in the absence of stone analysis.
- Levels above 30 mg/day are considered abnormal [544, 545].

4.9.2 **Specific treatment**

General preventative measures for fluid intake and diet are recommended. A diet low in methionine may theoretically reduce urinary excretion of cystine; however, patients are unlikely to comply sufficiently with such a diet. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption > 2 g/day [546].

A high level of diuresis is of fundamental importance, aiming for a 24-hour urine volume of > 3 L [547].

A considerable fluid intake evenly distributed throughout the day is necessary.

4.9.2.1 *Pharmacological treatment of cystine stones*

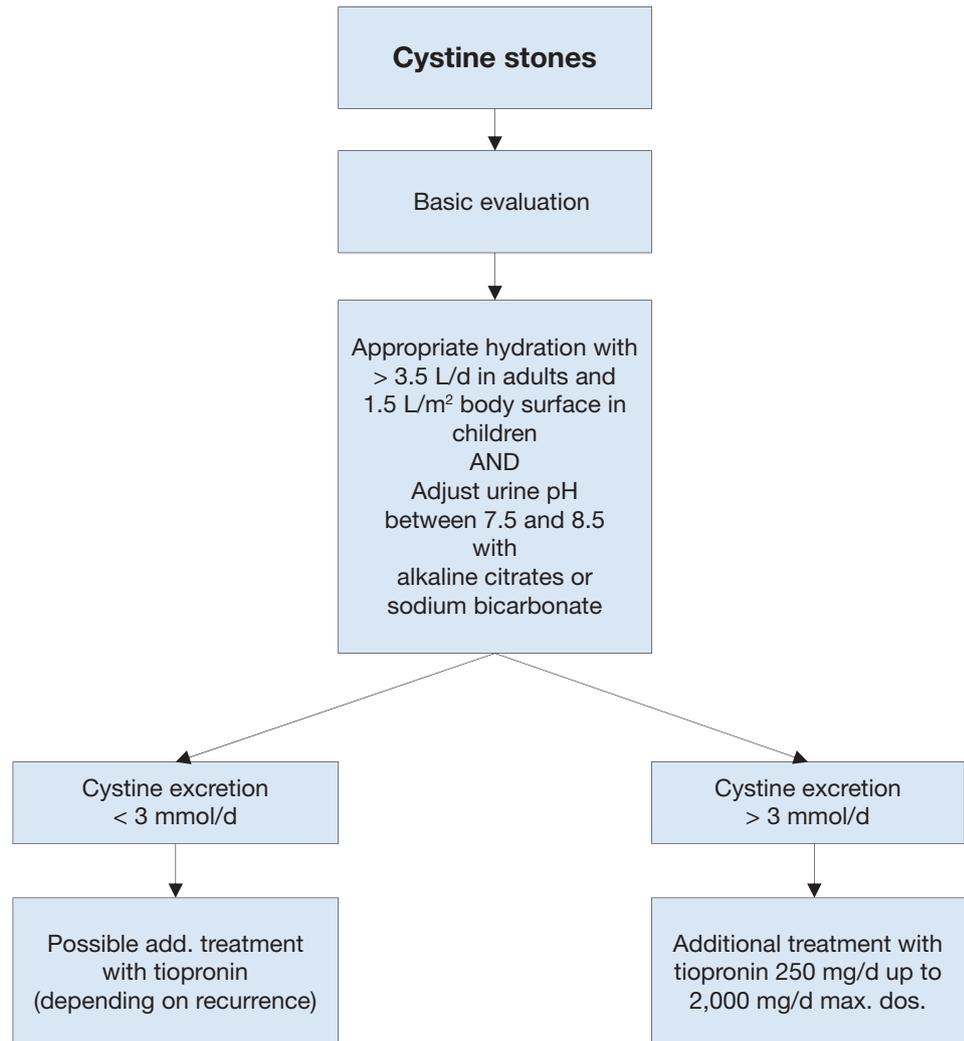
The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cystine solubility and ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m² body surface area in children.

Free cystine concentration can be decreased by reductive substances, which act by splitting the disulphide binding of cysteine.

Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example, when nephrotic syndrome develops, or poor compliance, especially with long-term use.

After carefully considering the risk of early tachyphylaxis, putting into place a dose-escape phenomenon for long-term use, and recurrence risk, tiopronin is recommended at cystine levels > 3.0 mmol/day or in the case of recurring stone formation, notwithstanding other preventive measures.

Figure 4.7: Metabolic management of cystine stones



4.9.3 Recommendations for the treatment of cystine stones

Therapeutic measures	LE	GR
Urine dilution Advise patients to increase their fluid intake so that 24-hour urine volume exceeds 3 L. Intake should be > 150 mL/h.	3	B
Alkalinisation For patients with cystine excretion < 3 mmol/day, prescribe potassium citrate 3-10 mmol two or three times daily, to achieve pH > 7.5.	3	B
Complex formation with cystine For patients with cystine excretion, > 3 mmol/day, or when other measures are insufficient: prescribe in addition to other measures tiopronin, 250-2,000 mg/day.	3	B

4.10 2,8-Dihydroxyadenine stones and xanthine stones [16]

All 2,8-Dihydroxyadenine and xanthine stone formers are considered to be at high risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones.

4.10.1 2,8-Dihydroxyadenine stones

A genetically determined defect of adenine phosphoribosyl transferase causes high urinary excretion of poorly soluble 2,8-Dihydroxyadenine. High-dose allopurinol or febuxostat are important options, but should be given with regular monitoring.

4.10.2 Xanthine stones

Patients who form xanthine stones usually show decreased levels of serum uric acid. There is no available pharmacological intervention.

4.10.3 Fluid intake and diet

Recommendations for general preventive measures apply. Pharmacological intervention is difficult, therefore, high fluid intake ensures optimal specific weight levels of urine < 1.010 . A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

4.11 Drug stones [49]

Drug stones are induced by pharmacological treatment [548] (Table 4.11). Two types exist:

- stones formed by crystallised compounds of the drug;
- stones formed due to unfavourable changes in urine composition under drug therapy.

Table 4.11: Compounds that cause drug stones

Active compounds crystallising in urine
Allopurinol/oxypurinol
Amoxicillin/ampicillin
Ceftriaxone
Quinolones
Ephedrine
Indinavir
Magnesium trisilicate
Sulphonamides
Triamterene
Zonisamide
Substances impairing urine composition
Acetazolamide
Allopurinol
Aluminium magnesium hydroxide
Ascorbic acid
Calcium
Furosemide
Laxatives
Methoxyflurane
Vitamin D
Topiramate

4.12 Matrix Stones

Pure matrix stones are extremely rare with less than 70 cases described in the literature. They are more prevalent in females. The main risk factors are recurrent UTIs, especially due to *Proteus mirabilis* or *Escherichia coli*, previous surgery for stone disease, chronic renal failure and haemodialysis. Complete endourological removal, frequently via the percutaneous approach, is critical. Given the rarity of matrix calculi a specific prophylactic regimen to minimise recurrence cannot be recommended. Eliminating infections and prophylactic use of antibiotics are most commonly proposed [233].

4.13 Unknown stone composition [15]

An accurate medical history is the first step towards identifying risk factors (Table 4.12).

Diagnostic imaging begins with US examination of both kidneys to establish whether the patient is stone free. Stone detection by US should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.

Blood analysis demonstrates severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children, hyperoxalaemia is additionally screened for.

Urinalysis is performed routinely with a dipstick test as described above. Urine culture is required if there are signs of infection.

Constant urine pH < 5.8 in the daily profile indicates acidic arrest, which may promote uric acid

crystallisation. Persistent urine pH > 5.8 in the daily profile indicates RTA, if UTI is excluded.

Microscopy of urinary sediment can help to discover rare stone types, because crystals of 2,8-Dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease. In cases in which the presence of cystine is doubtful, a cyanide nitroprusside colorimetric qualitative test can be used to detect the presence of cystine in urine, with a sensitivity of 72% and specificity of 95%. False-positive results are possible in patients with Fanconi's syndrome or homocystinuria, or in those taking various drugs, including ampicillin or sulfa-containing medication [549, 550].

Following this programme, the most probable stone type can be assumed and specific patient evaluation can follow. However, if any expelled stone material is available, it should be analysed by diagnostic confirmation or correction.

Table 4.12: Recommendations for the assessment of patients with stones of unknown composition

Investigation	Rationale for investigation
Take a medical history	<ul style="list-style-type: none"> • Stone history (former stone events, family history) • Dietary habits • Medication chart
Perform diagnostic imaging	<ul style="list-style-type: none"> • Ultrasound in the case of a suspected stone • Unenhanced helical computed tomography • Determination of Hounsfield units provides information about the possible stone composition
Perform a blood analysis	<ul style="list-style-type: none"> • Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid
Perform a urinalysis	<ul style="list-style-type: none"> • Urine pH profile (measurement after each voiding, minimum four times daily) • Dipstick test: leukocytes, erythrocytes, nitrite, protein, urine pH, specific weight • Urine cultures • Microscopy of urinary sediment (morning urine) • Cyanide nitroprusside test (cystine exclusion) <p>Further examinations depend on the results of the investigations listed above.</p>

5. REFERENCES

1. Skolarikos, A., *et al.* Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. *Eur Urol*, 2015. 67: 750.
<https://www.ncbi.nlm.nih.gov/pubmed/25454613>
2. Turk, C., *et al.* EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. *Eur Urol*, 2016. 69: 468.
<https://www.ncbi.nlm.nih.gov/pubmed/26318710>
3. Turk, C., *et al.* EAU Guidelines on Interventional Treatment for Urolithiasis. *Eur Urol*, 2016. 69: 475.
<https://www.ncbi.nlm.nih.gov/pubmed/26344917>
4. Hollingsworth, J.M., *et al.* Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. *BMJ*, 2016. 355: i6112.
<https://www.ncbi.nlm.nih.gov/pubmed/27908918>
5. Ruhayel, Y., *et al.* Tract sizes in miniaturized percutaneous nephrolithotomy: A systematic review. *Eur Urol* 2017. [No abstract available].
6. Drake, T. What are the benefits and harms of ureteroscopy (URS) compared with shock-wave lithotripsy (SWL) in the treatment of upper ureteral stones (UUS): A systematic review. *Eur Urol* 2017. [No abstract available].
7. Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>

8. Trinchieri A CG, *et al.*, Epidemiology, in Stone Disease, Segura JW, Khoury S, Pak CY, Preminger GM, Tolley D. Eds. 2003, Health Publications: Paris.
9. Stamatelou, K.K., *et al.* Time trends in reported prevalence of kidney stones in the United States: 1976-1994. *Kidney Int*, 2003. 63: 1817.
<https://www.ncbi.nlm.nih.gov/pubmed/12675858>
10. Hesse, A., *et al.* Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. *Eur Urol*, 2003. 44: 709.
<https://www.ncbi.nlm.nih.gov/pubmed/14644124>
11. Sanchez-Martin, F.M., *et al.* [Incidence and prevalence of published studies about urolithiasis in Spain. A review]. *Actas Urol Esp*, 2007. 31: 511.
<https://www.ncbi.nlm.nih.gov/pubmed/17711170>
12. Yasui, T., *et al.* 2082 Association of the loci 5q35.3, 7q14.3, and 13q14.1 with urolithiasis: A case-control study in the Japanese population, involving genome-wide association study. *J Urol*, 2013. 189: e854.
https://www.auanet.org/university/abstract_detail.cfm?id=2082&meetingID=13SAN
13. Strohmaier, W.L. Course of calcium stone disease without treatment. What can we expect? *Eur Urol*, 2000. 37: 339.
<https://www.ncbi.nlm.nih.gov/pubmed/10720863>
14. Keoghane, S., *et al.* The natural history of untreated renal tract calculi. *BJU Int*, 2010. 105: 1627.
<https://www.ncbi.nlm.nih.gov/pubmed/20438563>
15. Straub, M., *et al.* Diagnosis and metaphylaxis of stone disease. Consensus concept of the National Working Committee on Stone Disease for the upcoming German Urolithiasis Guideline. *World J Urol*, 2005. 23: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/16315051>
16. Hesse, A.T., *et al.* (Eds.), *Urinary Stones, Diagnosis, Treatment and Prevention of Recurrence*. 3rd edition. 2009, Basel.
17. Basiri, A., *et al.* Familial relations and recurrence pattern in nephrolithiasis: new words about old subjects. *Urol J*, 2010. 7: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/20535692>
18. Goldfarb, D.S., *et al.* A twin study of genetic and dietary influences on nephrolithiasis: a report from the Vietnam Era Twin (VET) Registry. *Kidney Int*, 2005. 67: 1053.
<https://www.ncbi.nlm.nih.gov/pubmed/15698445>
19. Asplin, J.R., *et al.* Hyperoxaluria in kidney stone formers treated with modern bariatric surgery. *J Urol*, 2007. 177: 565.
<https://www.ncbi.nlm.nih.gov/pubmed/17222634>
20. Gonzalez, R.D., *et al.* Kidney stone risk following modern bariatric surgery. *Curr Urol Rep*, 2014. 15: 401.
<https://www.ncbi.nlm.nih.gov/pubmed/24658828>
21. Rendina, D., *et al.* Metabolic syndrome and nephrolithiasis: a systematic review and meta-analysis of the scientific evidence. *J Nephrol*, 2014. 27: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/24696310>
22. Dell'Orto, V.G., *et al.* Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review. *Br J Clin Pharmacol*, 2014. 77: 958.
<https://www.ncbi.nlm.nih.gov/pubmed/24219102>
23. Mufti, U.B., *et al.* Nephrolithiasis in autosomal dominant polycystic kidney disease. *J Endourol*, 2010. 24: 1557.
<https://www.ncbi.nlm.nih.gov/pubmed/20818989>
24. Chen, Y., *et al.* Current trend and risk factors for kidney stones in persons with spinal cord injury: a longitudinal study. *Spinal Cord*, 2000. 38: 346.
<https://www.ncbi.nlm.nih.gov/pubmed/10889563>
25. Hara, A., *et al.* Incidence of nephrolithiasis in relation to environmental exposure to lead and cadmium in a population study. *Environ Res*, 2016. 145: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/26613344>
26. Leusmann, D.B., *et al.* Results of 5,035 stone analyses: a contribution to epidemiology of urinary stone disease. *Scand J Urol Nephrol*, 1990. 24: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/2237297>
27. Leusmann, D.B. Whewellite, weddellite and company: where do all the strange names originate? *BJU Int*, 2000. 86: 411.
<https://www.ncbi.nlm.nih.gov/pubmed/10971263>

28. Kim, S.C., *et al.* Cystine calculi: correlation of CT-visible structure, CT number, and stone morphology with fragmentation by shock wave lithotripsy. *Urol Res*, 2007. 35: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/17965956>
29. Wimpissinger, F., *et al.* The silence of the stones: asymptomatic ureteral calculi. *J Urol*, 2007. 178: 1341.
<https://www.ncbi.nlm.nih.gov/pubmed/17706721>
30. Ray, A.A., *et al.* Limitations to ultrasound in the detection and measurement of urinary tract calculi. *Urology*, 2010. 76: 295.
<https://www.ncbi.nlm.nih.gov/pubmed/20206970>
31. Smith-Bindman, R., *et al.* Ultrasonography versus computed tomography for suspected nephrolithiasis. *N Engl J Med*, 2014. 371: 1100.
<https://www.ncbi.nlm.nih.gov/pubmed/25229916>
32. Heidenreich, A., *et al.* Modern approach of diagnosis and management of acute flank pain: review of all imaging modalities. *Eur Urol*, 2002. 41: 351.
<https://www.ncbi.nlm.nih.gov/pubmed/12074804>
33. Kennish, S.J., *et al.* Is the KUB radiograph redundant for investigating acute ureteric colic in the non-contrast enhanced computed tomography era? *Clin Radiol*, 2008. 63: 1131.
<https://www.ncbi.nlm.nih.gov/pubmed/18774360>
34. Worster, A., *et al.* The accuracy of noncontrast helical computed tomography versus intravenous pyelography in the diagnosis of suspected acute urolithiasis: a meta-analysis. *Ann Emerg Med*, 2002. 40: 280.
<https://www.ncbi.nlm.nih.gov/pubmed/12192351>
35. Wu, D.S., *et al.* Indinavir urolithiasis. *Curr Opin Urol*, 2000. 10: 557.
<https://www.ncbi.nlm.nih.gov/pubmed/11148725>
36. El-Nahas, A.R., *et al.* A prospective multivariate analysis of factors predicting stone disintegration by extracorporeal shock wave lithotripsy: the value of high-resolution noncontrast computed tomography. *Eur Urol*, 2007. 51: 1688.
<https://www.ncbi.nlm.nih.gov/pubmed/17161522>
37. Patel, T., *et al.* Skin to stone distance is an independent predictor of stone-free status following shockwave lithotripsy. *J Endourol*, 2009. 23: 1383.
<https://www.ncbi.nlm.nih.gov/pubmed/19694526>
38. Zarse, C.A., *et al.* CT visible internal stone structure, but not Hounsfield unit value, of calcium oxalate monohydrate (COM) calculi predicts lithotripsy fragility in vitro. *Urol Res*, 2007. 35: 201.
<https://www.ncbi.nlm.nih.gov/pubmed/17565491>
39. Kluner, C., *et al.* Does ultra-low-dose CT with a radiation dose equivalent to that of KUB suffice to detect renal and ureteral calculi? *J Comput Assist Tomogr*, 2006. 30: 44.
<https://www.ncbi.nlm.nih.gov/pubmed/16365571>
40. Caoili, E.M., *et al.* Urinary tract abnormalities: initial experience with multi-detector row CT urography. *Radiology*, 2002. 222: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/11818599>
41. Van Der Molen, A.J., *et al.* CT urography: definition, indications and techniques. A guideline for clinical practice. *Eur Radiol*, 2008. 18: 4.
<https://www.ncbi.nlm.nih.gov/pubmed/17973110>
42. Thomson, J.M., *et al.* Computed tomography versus intravenous urography in diagnosis of acute flank pain from urolithiasis: a randomized study comparing imaging costs and radiation dose. *Australas Radiol*, 2001. 45: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/11531751>
43. Smith-Bindman, R., *et al.* Computed Tomography Radiation Dose in Patients With Suspected Urolithiasis. *JAMA Intern Med*, 2015. 175: 1413.
<https://www.ncbi.nlm.nih.gov/pubmed/26121191>
44. Jellison, F.C., *et al.* Effect of low dose radiation computerized tomography protocols on distal ureteral calculus detection. *J Urol*, 2009. 182: 2762.
<https://www.ncbi.nlm.nih.gov/pubmed/19837431>
45. Poletti, P.A., *et al.* Low-dose versus standard-dose CT protocol in patients with clinically suspected renal colic. *AJR Am J Roentgenol*, 2007. 188: 927.
<https://www.ncbi.nlm.nih.gov/pubmed/17377025>
46. Niemann, T., *et al.* Diagnostic performance of low-dose CT for the detection of urolithiasis: a meta-analysis. *AJR Am J Roentgenol*, 2008. 191: 396.
<https://www.ncbi.nlm.nih.gov/pubmed/18647908>

47. Zheng, X., *et al.* Dual-energy computed tomography for characterizing urinary calcified calculi and uric acid calculi: A meta-analysis. *Eur J Radiol*, 2016. 85: 1843.
<https://www.ncbi.nlm.nih.gov/pubmed/27666626>
48. El-Wahab, O.A., *et al.* Multislice computed tomography vs. intravenous urography for planning supine percutaneous nephrolithotomy: A randomised clinical trial. *Arab J Urol*, 2014. 12: 162.
<https://www.ncbi.nlm.nih.gov/pubmed/26019942>
49. Pearle, M.S., *et al.*, Medical management of urolithiasis. 2nd International consultation on Stone Disease, ed. K.S. Denstedt J. 2008.
50. Bonkat, G., *et al.*, EAU Guidelines on Urological Infections, in EAU Guidelines, Edn. published as the 32nd EAU Annual Meeting, London, E.A.o.U.G. Office, Editor. 2017, European Association of Urology Guidelines Office: Arnhem, The Netherlands.
51. Mandel, N., *et al.* Conversion of calcium oxalate to calcium phosphate with recurrent stone episodes. *J Urol*, 2003. 169: 2026.
<https://www.ncbi.nlm.nih.gov/pubmed/12771710>
52. Hesse, A., *et al.* Quality control in urinary stone analysis: results of 44 ring trials (1980-2001). *Clin Chem Lab Med*, 2005. 43: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/15843235>
53. Sutor, D.J., *et al.* Identification standards for human urinary calculus components, using crystallographic methods. *Br J Urol*, 1968. 40: 22.
<https://www.ncbi.nlm.nih.gov/pubmed/5642759>
54. Abdel-Halim, R.E., *et al.* A review of urinary stone analysis techniques. *Saudi Med J*, 2006. 27: 1462.
<https://www.ncbi.nlm.nih.gov/pubmed/17013464>
55. Swartz, M.A., *et al.* Admission for nephrolithiasis in pregnancy and risk of adverse birth outcomes. *Obstet Gynecol*, 2007. 109: 1099.
<https://www.ncbi.nlm.nih.gov/pubmed/17470589>
56. Patel, S.J., *et al.* Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. *Radiographics*, 2007. 27: 1705.
<https://www.ncbi.nlm.nih.gov/pubmed/18025513>
57. Asrat, T., *et al.* Ultrasonographic detection of ureteral jets in normal pregnancy. *Am J Obstet Gynecol*, 1998. 178: 1194.
<https://www.ncbi.nlm.nih.gov/pubmed/9662301>
58. Roy, C., *et al.* Assessment of painful ureterohydronephrosis during pregnancy by MR urography. *Eur Radiol*, 1996. 6: 334.
<https://www.ncbi.nlm.nih.gov/pubmed/8798002>
59. Juan, Y.S., *et al.* Management of symptomatic urolithiasis during pregnancy. *Kaohsiung J Med Sci*, 2007. 23: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/17525006>
60. Cody, D.D., *et al.* Strategies for formulating appropriate MDCT techniques when imaging the chest, abdomen, and pelvis in pediatric patients. *AJR Am J Roentgenol*, 2004. 182: 849.
<https://www.ncbi.nlm.nih.gov/pubmed/15039151>
61. Masselli, G., *et al.* Stone disease in pregnancy: imaging-guided therapy. *Insights Imaging*, 2014. 5: 691.
<https://www.ncbi.nlm.nih.gov/pubmed/25249333>
62. Sternberg, K., *et al.* Pediatric stone disease: an evolving experience. *J Urol*, 2005. 174: 1711.
<https://www.ncbi.nlm.nih.gov/pubmed/16148688>
63. Palmer, L.S. Pediatric urologic imaging. *Urol Clin North Am*, 2006. 33: 409.
<https://www.ncbi.nlm.nih.gov/pubmed/16829274>
64. Passerotti, C., *et al.* Ultrasound versus computerized tomography for evaluating urolithiasis. *J Urol*, 2009. 182: 1829.
<https://www.ncbi.nlm.nih.gov/pubmed/19692054>
65. Tasian, G.E., *et al.* Evaluation and medical management of kidney stones in children. *J Urol*, 2014. 192: 1329.
<https://www.ncbi.nlm.nih.gov/pubmed/24960469>
66. Riccabona, M., *et al.* Imaging recommendations in paediatric urology. Minutes of the ESPR urology task force session on childhood obstructive uropathy, high-grade fetal hydronephrosis, childhood haematuria, and urolithiasis in childhood. ESPR Annual Congress, Edinburgh, UK, June 2008. *Pediatr Radiol*, 2009. 39: 891.
<https://www.ncbi.nlm.nih.gov/pubmed/19565235>

67. Darge, K., *et al.* [Modern ultrasound technologies and their application in pediatric urinary tract imaging]. *Radiologe*, 2005. 45: 1101.
<https://www.ncbi.nlm.nih.gov/pubmed/16086170>
68. Pepe, P., *et al.* Functional evaluation of the urinary tract by color-Doppler ultrasonography (CDU) in 100 patients with renal colic. *Eur J Radiol*, 2005. 53: 131.
<https://www.ncbi.nlm.nih.gov/pubmed/15607864>
69. Oner, S., *et al.* Comparison of spiral CT and US in the evaluation of pediatric urolithiasis. *Jbr-btr*, 2004. 87: 219. 15587558
<https://www.ncbi.nlm.nih.gov/pubmed/>
70. Palmer, J.S., *et al.* Diagnosis of pediatric urolithiasis: role of ultrasound and computerized tomography. *J Urol*, 2005. 174: 1413.
<https://www.ncbi.nlm.nih.gov/pubmed/16145452>
71. Riccabona, M., *et al.* Conventional imaging in paediatric urology. *Eur J Radiol*, 2002. 43: 100.
<https://www.ncbi.nlm.nih.gov/pubmed/12127207>
72. Chateil, J.F., *et al.* [Practical measurement of radiation dose in pediatric radiology: use of the dose surface product in digital fluoroscopy and for neonatal chest radiographs]. *J Radiol*, 2004. 85: 619.
<https://www.ncbi.nlm.nih.gov/pubmed/15205653>
73. Stratton, K.L., *et al.* Implications of ionizing radiation in the pediatric urology patient. *J Urol*, 2010. 183: 2137.
<https://www.ncbi.nlm.nih.gov/pubmed/20399463>
74. Tamm, E.P., *et al.* Evaluation of the patient with flank pain and possible ureteral calculus. *Radiology*, 2003. 228: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/12819343>
75. Leppert, A., *et al.* Impact of magnetic resonance urography on preoperative diagnostic workup in children affected by hydronephrosis: should IVU be replaced? *J Pediatr Surg*, 2002. 37: 1441.
<https://www.ncbi.nlm.nih.gov/pubmed/12378450>
76. Phillips, E., *et al.* Emergency room management of ureteral calculi: current practices. *J Endourol*, 2009. 23: 1021.
<https://www.ncbi.nlm.nih.gov/pubmed/19445640>
77. Engeler, D.S., *et al.* The ideal analgesic treatment for acute renal colic--theory and practice. *Scand J Urol Nephrol*, 2008. 42: 137.
<https://www.ncbi.nlm.nih.gov/pubmed/17899475>
78. Shokeir, A.A., *et al.* Resistive index in renal colic: the effect of nonsteroidal anti-inflammatory drugs. *BJU Int*, 1999. 84: 249.
<https://www.ncbi.nlm.nih.gov/pubmed/10468715>
79. Afshar, K., *et al.* Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic. *Cochrane Database Syst Rev*, 2015: CD006027.
<https://www.ncbi.nlm.nih.gov/pubmed/26120804>
80. Krum, H., *et al.* Blood pressure and cardiovascular outcomes in patients taking nonsteroidal antiinflammatory drugs. *Cardiovasc Ther*, 2012. 30: 342.
<https://www.ncbi.nlm.nih.gov/pubmed/21884017>
81. Bhala, N., *et al.* Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*, 2013. 382: 769.
<https://www.ncbi.nlm.nih.gov/pubmed/23726390>
82. Holdgate, A., *et al.* Nonsteroidal anti-inflammatory drugs (NSAIDs) versus opioids for acute renal colic. *Cochrane Database Syst Rev*, 2005: CD004137.
<https://www.ncbi.nlm.nih.gov/pubmed/15846699>
83. Holdgate, A., *et al.* Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *BMJ*, 2004. 328: 1401.
<https://www.ncbi.nlm.nih.gov/pubmed/15178585>
84. Seitz, C., *et al.* Medical therapy to facilitate the passage of stones: what is the evidence? *Eur Urol*, 2009. 56: 455.
<https://www.ncbi.nlm.nih.gov/pubmed/19560860>
85. Lee, A., *et al.* Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. *Cochrane Database Syst Rev*, 2007: CD002765.
<https://www.ncbi.nlm.nih.gov/pubmed/17443518>
86. Laerum, E., *et al.* Oral diclofenac in the prophylactic treatment of recurrent renal colic. A double-blind comparison with placebo. *Eur Urol*, 1995. 28: 108.
<https://www.ncbi.nlm.nih.gov/pubmed/8529732>

87. Pickard, R., *et al.* Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet*, 2015. 386: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/25998582>
88. Furyk, J.S., *et al.* Distal Ureteric Stones and Tamsulosin: A Double-Blind, Placebo-Controlled, Randomized, Multicenter Trial. *Ann Emerg Med*, 2016. 67: 86.
<https://www.ncbi.nlm.nih.gov/pubmed/26194935>
89. Ramsey, S., *et al.* Evidence-based drainage of infected hydronephrosis secondary to ureteric calculi. *J Endourol*, 2010. 24: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/20063999>
90. Lynch, M.F., *et al.* Percutaneous nephrostomy and ureteric stent insertion for acute renal deobstruction: Consensus based guidance. *Brit J Med Surg Urol*, 2008. 1: 120.
<http://www.sciencedirect.com/science/article/pii/S1875974208000955>
91. Pearle, M.S., *et al.* Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi. *J Urol*, 1998. 160: 1260.
<https://www.ncbi.nlm.nih.gov/pubmed/9751331>
92. Wang, C.J., *et al.* Percutaneous nephrostomy versus ureteroscopic management of sepsis associated with ureteral stone impaction: a randomized controlled trial. *Urolithiasis*, 2016. 44: 415.
<https://www.ncbi.nlm.nih.gov/pubmed/26662171>
93. ElSheemy, M.S., *et al.* Ureteric stents vs percutaneous nephrostomy for initial urinary drainage in children with obstructive anuria and acute renal failure due to ureteric calculi: a prospective, randomised study. *BJU Int*, 2015. 115: 473.
<https://www.ncbi.nlm.nih.gov/pubmed/24698195>
94. Marien, T., *et al.* Antimicrobial resistance patterns in cases of obstructive pyelonephritis secondary to stones. *Urology*, 2015. 85: 64.
<https://www.ncbi.nlm.nih.gov/pubmed/25530365>
95. Lo, C.W., *et al.* Effectiveness of Prophylactic Antibiotics against Post-Ureteroscopic Lithotripsy Infections: Systematic Review and Meta-Analysis. *Surg Infect (Larchmt)*, 2015. 16: 415.
<https://www.ncbi.nlm.nih.gov/pubmed/26207401>
96. Grabe, M. Antimicrobial agents in transurethral prostatic resection. *J Urol*, 1987. 138: 245.
<https://www.ncbi.nlm.nih.gov/pubmed/3298693>
97. Gravas, S., *et al.* Postoperative infection rates in low risk patients undergoing percutaneous nephrolithotomy with and without antibiotic prophylaxis: a matched case control study. *J Urol*, 2012. 188: 843.
<https://www.ncbi.nlm.nih.gov/pubmed/22819398>
98. Hsieh, C.H., *et al.* Are prophylactic antibiotics necessary in patients with preoperative sterile urine undergoing ureterorenoscopic lithotripsy? *BJU Int*, 2014. 113: 275.
<https://www.ncbi.nlm.nih.gov/pubmed/24127851>
99. Klingler, H.C., *et al.* Stone treatment and coagulopathy. *Eur Urol*, 2003. 43: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/12507547>
100. Kefer, J.C., *et al.* Safety and efficacy of percutaneous nephrostolithotomy in patients on anticoagulant therapy. *J Urol*, 2009. 181: 144.
<https://www.ncbi.nlm.nih.gov/pubmed/18289567>
101. Baron, T.H., *et al.* Management of antithrombotic therapy in patients undergoing invasive procedures. *N Engl J Med*, 2013. 368: 2113.
<https://www.ncbi.nlm.nih.gov/pubmed/23718166>
102. Naspro, R., *et al.* Antiplatelet therapy in patients with coronary stent undergoing urologic surgery: is it still no man's land? *Eur Urol*, 2013. 64: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/23428067>
103. Eberli, D., *et al.* Urological surgery and antiplatelet drugs after cardiac and cerebrovascular accidents. *J Urol*, 2010. 183: 2128.
<https://www.ncbi.nlm.nih.gov/pubmed/20399452>
104. Razvi, H., *et al.* Risk factors for perinephric hematoma formation after shockwave lithotripsy: a matched case-control analysis. *J Endourol*, 2012. 26: 1478.
<https://www.ncbi.nlm.nih.gov/pubmed/22712655>
105. Rassweiler, J.J., *et al.* Treatment of renal stones by extracorporeal shockwave lithotripsy: an update. *Eur Urol*, 2001. 39: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/11223679>

106. Fischer, C., *et al.* [Extracorporeal shock-wave lithotripsy induced ultrastructural changes to the renal parenchyma under aspirin use. Electron microscopic findings in the rat kidney]. *Urologe A*, 2007. 46: 150.
<https://www.ncbi.nlm.nih.gov/pubmed/17221245>
107. Becopoulos, T., *et al.* Extracorporeal lithotripsy in patients with hemophilia. *Eur Urol*, 1988. 14: 343.
<https://www.ncbi.nlm.nih.gov/pubmed/3169076>
108. Ishikawa, J., *et al.* Extracorporeal shock wave lithotripsy in von Willebrand's disease. *Int J Urol*, 1996. 3: 58.
<https://www.ncbi.nlm.nih.gov/pubmed/8646601>
109. Zanetti, G., *et al.* Extracorporeal shockwave lithotripsy in patients treated with antithrombotic agents. *J Endourol*, 2001. 15: 237.
<https://www.ncbi.nlm.nih.gov/pubmed/11339387>
110. Schnabel, M.J., *et al.* Incidence and risk factors of renal hematoma: a prospective study of 1,300 SWL treatments. *Urolithiasis*, 2014. 42: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/24419328>
111. Schnabel, M.J., *et al.* Antiplatelet and anticoagulative medication during shockwave lithotripsy. *J Endourol*, 2014. 28: 1034.
<https://www.ncbi.nlm.nih.gov/pubmed/24851726>
112. Turna, B., *et al.* Safety and efficacy of flexible ureterorenoscopy and holmium:YAG lithotripsy for intrarenal stones in anticoagulated cases. *J Urol*, 2008. 179: 1415.
<https://www.ncbi.nlm.nih.gov/pubmed/18289567>
113. Toepfer, N.J., *et al.* The effect of antiplatelet and anticoagulant therapy on the clinical outcome of patients undergoing ureteroscopy. *Urology*, 2013. 82: 773.
<https://www.ncbi.nlm.nih.gov/pubmed/23876586>
114. Aboumarzouk, O.M., *et al.* Flexible ureteroscopy and holmium:YAG laser lithotripsy for stone disease in patients with bleeding diathesis: a systematic review of the literature. *Int Braz J Urol*, 2012. 38: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/22765861>
115. Watterson, J.D., *et al.* Safety and efficacy of holmium: YAG laser lithotripsy in patients with bleeding diatheses. *J Urol*, 2002. 168: 442.
<https://www.ncbi.nlm.nih.gov/pubmed/12131284>
116. Elkoushy, M.A., *et al.* Ureteroscopy in patients with coagulopathies is associated with lower stone-free rate and increased risk of clinically significant hematuria. *Int Braz J Urol*, 2012. 38: 195.
<https://www.ncbi.nlm.nih.gov/pubmed/22555043>
117. Kuo, R.L., *et al.* Use of ureteroscopy and holmium:YAG laser in patients with bleeding diatheses. *Urology*, 1998. 52: 609.
<https://www.ncbi.nlm.nih.gov/pubmed/9763079>
118. Gupta, A.D., *et al.* Coronary stent management in elective genitourinary surgery. *BJU Int*, 2012. 110: 480.
<https://www.ncbi.nlm.nih.gov/pubmed/22192977>
119. Coptcoat, M.J., *et al.* The steinstrasse: a legacy of extracorporeal lithotripsy? *Eur Urol*, 1988. 14: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/3360043>
120. Ather, M.H., *et al.* Does ureteral stenting prior to shock wave lithotripsy influence the need for intervention in steinstrasse and related complications? *Urol Int*, 2009. 83: 222.
<https://www.ncbi.nlm.nih.gov/pubmed/19752621>
121. Lucio, J., 2nd, *et al.* Steinstrasse predictive factors and outcomes after extracorporeal shockwave lithotripsy. *Int Braz J Urol*, 2011. 37: 477.
<https://www.ncbi.nlm.nih.gov/pubmed/21888699>
122. Musa, A.A. Use of double-J stents prior to extracorporeal shock wave lithotripsy is not beneficial: results of a prospective randomized study. *Int Urol Nephrol*, 2008. 40: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/17394095>
123. Mohayuddin, N., *et al.* The outcome of extracorporeal shockwave lithotripsy for renal pelvic stone with and without JJ stent--a comparative study. *J Pak Med Assoc*, 2009. 59: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/19288938>
124. Shen, P., *et al.* Use of ureteral stent in extracorporeal shock wave lithotripsy for upper urinary calculi: a systematic review and meta-analysis. *J Urol*, 2011. 186: 1328.
<https://www.ncbi.nlm.nih.gov/pubmed/21855945>
125. Moursy, E., *et al.* Tamsulosin as an expulsive therapy for steinstrasse after extracorporeal shock wave lithotripsy: a randomized controlled study. *Scand J Urol Nephrol*, 2010. 44: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/20560802>

126. Resim, S., *et al.* Role of tamsulosin in treatment of patients with steinstrasse developing after extracorporeal shock wave lithotripsy. *Urology*, 2005. 66: 945.
<https://www.ncbi.nlm.nih.gov/pubmed/16286100>
127. Goyal, R., *et al.* Does the type of steinstrasse predict the outcome of expectant therapy? *Indian J Urol*, 2006. 22: 135.
<http://indianjurol.com/article.asp?issn=0970-1591;year=2006;volume=22;issue=2;spage=135;epage=138;aualast=Goyal>
128. Rabbani, S.M. Treatment of steinstrasse by transureteral lithotripsy. *Urol J*, 2008. 5: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/18592460>
129. Inci, K., *et al.* Prospective long-term followup of patients with asymptomatic lower pole caliceal stones. *J Urol*, 2007. 177: 2189.
<https://www.ncbi.nlm.nih.gov/pubmed/17509315>
130. Bernardo, N.O., *et al.* Chemolysis of urinary calculi. *Urol Clin North Am*, 2000. 27: 355.
<https://www.ncbi.nlm.nih.gov/pubmed/10778477>
131. Chughtai, M.N., *et al.* Management of uric acid stone. *J Pak Med Assoc*, 1992. 42: 153.
<https://www.ncbi.nlm.nih.gov/pubmed/1404830>
132. Tiselius, H.G., *et al.* Minimally invasive treatment of infection staghorn stones with shock wave lithotripsy and chemolysis. *Scand J Urol Nephrol*, 1999. 33: 286.
<https://www.ncbi.nlm.nih.gov/pubmed/10572989>
133. Becker, G. Uric acid stones. *Nephrology*, 2007. 12: S21.
<http://dx.doi.org/10.1111/j.1440-1797.2007.00774.x>
134. El-Gamal, O., *et al.* Role of combined use of potassium citrate and tamsulosin in the management of uric acid distal ureteral calculi. *Urol Res*, 2012. 40: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/21858663>
135. Ohmori, K., *et al.* Effects of shock waves on the mouse fetus. *J Urol*, 1994. 151: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/8254823>
136. Stroom, S.B., *et al.* Extracorporeal shock wave lithotripsy in patients with bleeding diatheses. *J Urol*, 1990. 144: 1347.
<https://www.ncbi.nlm.nih.gov/pubmed/1613866>
137. Carey, S.W., *et al.* Extracorporeal shock wave lithotripsy for patients with calcified ipsilateral renal arterial or abdominal aortic aneurysms. *J Urol*, 1992. 148: 18.
<https://www.ncbi.nlm.nih.gov/pubmed/1613866>
138. Platonov, M.A., *et al.* Pacemakers, implantable cardioverter/defibrillators, and extracorporeal shockwave lithotripsy: evidence-based guidelines for the modern era. *J Endourol*, 2008. 22: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/18294028>
139. Li, W.M., *et al.* Clinical predictors of stone fragmentation using slow-rate shock wave lithotripsy. *Urol Int*, 2007. 79: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/17851280>
140. Yilmaz, E., *et al.* Optimal frequency in extracorporeal shock wave lithotripsy: prospective randomized study. *Urology*, 2005. 66: 1160.
<https://www.ncbi.nlm.nih.gov/pubmed/16360432>
141. Pace, K.T., *et al.* Shock wave lithotripsy at 60 or 120 shocks per minute: a randomized, double-blind trial. *J Urol*, 2005. 174: 595.
<https://www.ncbi.nlm.nih.gov/pubmed/16006908>
142. Madbouly, K., *et al.* Slow versus fast shock wave lithotripsy rate for urolithiasis: a prospective randomized study. *J Urol*, 2005. 173: 127.
<https://www.ncbi.nlm.nih.gov/pubmed/15592053>
143. Semins, M.J., *et al.* The effect of shock wave rate on the outcome of shock wave lithotripsy: a meta-analysis. *J Urol*, 2008. 179: 194.
<https://www.ncbi.nlm.nih.gov/pubmed/18001796>
144. Li, K., *et al.* Optimal frequency of shock wave lithotripsy in urolithiasis treatment: a systematic review and meta-analysis of randomized controlled trials. *J Urol*, 2013. 190: 1260.
<https://www.ncbi.nlm.nih.gov/pubmed/23538240>
145. Nguyen, D.P., *et al.* Optimization of Extracorporeal Shock Wave Lithotripsy Delivery Rates Achieves Excellent Outcomes for Ureteral Stones: Results of a Prospective Randomized Trial. *J Urol*, 2015. 194: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/25661296>
146. Pishchalnikov, Y.A., *et al.* Why stones break better at slow shockwave rates than at fast rates: in vitro study with a research electrohydraulic lithotripter. *J Endourol*, 2006. 20: 537.
<https://www.ncbi.nlm.nih.gov/pubmed/16903810>

147. Connors, B.A., *et al.* Extracorporeal shock wave lithotripsy at 60 shock waves/min reduces renal injury in a porcine model. *BJU Int*, 2009. 104: 1004.
<https://www.ncbi.nlm.nih.gov/pubmed/19338532>
148. Moon, K.B., *et al.* Optimal shock wave rate for shock wave lithotripsy in urolithiasis treatment: a prospective randomized study. *Korean J Urol*, 2012. 53: 790.
<https://www.ncbi.nlm.nih.gov/pubmed/23185672>
149. Ng, C.F., *et al.* A prospective, randomized study of the clinical effects of shock wave delivery for unilateral kidney stones: 60 versus 120 shocks per minute. *J Urol*, 2012. 188: 837.
<https://www.ncbi.nlm.nih.gov/pubmed/22819406>
150. Kang, D.H., *et al.* Comparison of High, Intermediate, and Low Frequency Shock Wave Lithotripsy for Urinary Tract Stone Disease: Systematic Review and Network Meta-Analysis. *PLoS One*, 2016. 11: e0158661.
<https://www.ncbi.nlm.nih.gov/pubmed/27387279>
151. Connors, B.A., *et al.* Effect of initial shock wave voltage on shock wave lithotripsy-induced lesion size during step-wise voltage ramping. *BJU Int*, 2009. 103: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/18680494>
152. Handa, R.K., *et al.* Optimising an escalating shockwave amplitude treatment strategy to protect the kidney from injury during shockwave lithotripsy. *BJU Int*, 2012. 110: E1041.
<https://www.ncbi.nlm.nih.gov/pubmed/22612388>
153. Skuginna, V., *et al.* Does Stepwise Voltage Ramping Protect the Kidney from Injury During Extracorporeal Shockwave Lithotripsy? Results of a Prospective Randomized Trial. *Eur Urol*, 2016. 69: 267.
<https://www.ncbi.nlm.nih.gov/pubmed/26119561>
154. Maloney, M.E., *et al.* Progressive increase of lithotripter output produces better in-vivo stone comminution. *J Endourol*, 2006. 20: 603.
<https://www.ncbi.nlm.nih.gov/pubmed/16999607>
155. Demirci, D., *et al.* Comparison of conventional and step-wise shockwave lithotripsy in management of urinary calculi. *J Endourol*, 2007. 21: 1407.
<https://www.ncbi.nlm.nih.gov/pubmed/18044996>
156. Honey, R.J., *et al.* Shock wave lithotripsy: a randomized, double-blind trial to compare immediate versus delayed voltage escalation. *Urology*, 2010. 75: 38.
<https://www.ncbi.nlm.nih.gov/pubmed/19896176>
157. Pishchalnikov, Y.A., *et al.* Air pockets trapped during routine coupling in dry head lithotripsy can significantly decrease the delivery of shock wave energy. *J Urol*, 2006. 176: 2706.
<https://www.ncbi.nlm.nih.gov/pubmed/17085200>
158. Jain, A., *et al.* Effect of air bubbles in the coupling medium on efficacy of extracorporeal shock wave lithotripsy. *Eur Urol*, 2007. 51: 1680.
<https://www.ncbi.nlm.nih.gov/pubmed/17112655>
159. Logarakis, N.F., *et al.* Variation in clinical outcome following shock wave lithotripsy. *J Urol*, 2000. 163: 721.
<https://www.ncbi.nlm.nih.gov/pubmed/10687964>
160. Eichel, L., *et al.* Operator experience and adequate anesthesia improve treatment outcome with third-generation lithotripters. *J Endourol*, 2001. 15: 671.
<https://www.ncbi.nlm.nih.gov/pubmed/11697394>
161. Sorensen, C., *et al.* Comparison of intravenous sedation versus general anesthesia on the efficacy of the Doli 50 lithotripter. *J Urol*, 2002. 168: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/12050487>
162. Cleveland, R.O., *et al.* Effect of stone motion on in vitro comminution efficiency of Storz Modulith SLX. *J Endourol*, 2004. 18: 629.
<https://www.ncbi.nlm.nih.gov/pubmed/15597649>
163. Honey, R.J., *et al.* A prospective study examining the incidence of bacteriuria and urinary tract infection after shock wave lithotripsy with targeted antibiotic prophylaxis. *J Urol*, 2013. 189: 2112.
<https://www.ncbi.nlm.nih.gov/pubmed/23276509>
164. Lu, Y., *et al.* Antibiotic prophylaxis for shock wave lithotripsy in patients with sterile urine before treatment may be unnecessary: a systematic review and meta-analysis. *J Urol*, 2012. 188: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/22704118>
165. Chen, K., *et al.* The Efficacy and Safety of Tamsulosin Combined with Extracorporeal Shockwave Lithotripsy for Urolithiasis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Endourol*, 2015. 29: 1166.
<https://www.ncbi.nlm.nih.gov/pubmed/25915454>

166. Naja, V., *et al.* Tamsulosin facilitates earlier clearance of stone fragments and reduces pain after shockwave lithotripsy for renal calculi: results from an open-label randomized study. *Urology*, 2008. 72: 1006.
<https://www.ncbi.nlm.nih.gov/pubmed/18799202>
167. Zhu, Y., *et al.* Alpha-Blockers to assist stone clearance after extracorporeal shock wave lithotripsy: a meta-analysis. *BJU Int*, 2010. 106: 256.
<https://www.ncbi.nlm.nih.gov/pubmed/19889063>
168. Zheng, S., *et al.* Tamsulosin as adjunctive treatment after shockwave lithotripsy in patients with upper urinary tract stones: a systematic review and meta-analysis. *Scand J Urol Nephrol*, 2010. 44: 425.
<https://www.ncbi.nlm.nih.gov/pubmed/21080841>
169. Schuler, T.D., *et al.* Medical expulsive therapy as an adjunct to improve shockwave lithotripsy outcomes: a systematic review and meta-analysis. *J Endourol*, 2009. 23: 387.
<https://www.ncbi.nlm.nih.gov/pubmed/19245302>
170. Li, M., *et al.* Adjunctive medical therapy with alpha-blocker after extracorporeal shock wave lithotripsy of renal and ureteral stones: a meta-analysis. *PLoS One*, 2015. 10: e0122497.
<https://www.ncbi.nlm.nih.gov/pubmed/25860144>
171. Skolarikos, A., *et al.* The Efficacy of Medical Expulsive Therapy (MET) in Improving Stone-free Rate and Stone Expulsion Time, After Extracorporeal Shock Wave Lithotripsy (SWL) for Upper Urinary Stones: A Systematic Review and Meta-analysis. *Urology*, 2015. 86: 1057.
<https://www.ncbi.nlm.nih.gov/pubmed/26383613>
172. De Nunzio, C., *et al.* Tamsulosin or Silodosin Adjuvant Treatment Is Ineffective in Improving Shockwave Lithotripsy Outcome: A Short-Term Follow-Up Randomized, Placebo-Controlled Study. *J Endourol*, 2016. 30: 817.
<https://www.ncbi.nlm.nih.gov/pubmed/27080916>
173. Pearle, M.S., *et al.* Prospective, randomized trial comparing shock wave lithotripsy and ureteroscopy for lower pole caliceal calculi 1 cm or less. *J Urol*, 2005. 173: 2005.
<https://www.ncbi.nlm.nih.gov/pubmed/15879805>
174. Lingeman, J.E., *et al.* Comparison of results and morbidity of percutaneous nephrostolithotomy and extracorporeal shock wave lithotripsy. *J Urol*, 1987. 138: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/3625845>
175. Madbouly, K., *et al.* Risk factors for the formation of a steinstrasse after extracorporeal shock wave lithotripsy: a statistical model. *J Urol*, 2002. 167: 1239.
<https://www.ncbi.nlm.nih.gov/pubmed/11832705>
176. Sayed, M.A., *et al.* Steinstrasse after extracorporeal shockwave lithotripsy: aetiology, prevention and management. *BJU Int*, 2001. 88: 675.
<https://www.ncbi.nlm.nih.gov/pubmed/11890235>
177. Skolarikos, A., *et al.* Extracorporeal shock wave lithotripsy 25 years later: complications and their prevention. *Eur Urol*, 2006. 50: 981.
<https://www.ncbi.nlm.nih.gov/pubmed/16481097>
178. Osman, M.M., *et al.* 5-year-follow-up of patients with clinically insignificant residual fragments after extracorporeal shockwave lithotripsy. *Eur Urol*, 2005. 47: 860.
<https://www.ncbi.nlm.nih.gov/pubmed/15925084>
179. Tan, Y.M., *et al.* Clinical experience and results of ESWL treatment for 3,093 urinary calculi with the Storz Modulith SL 20 lithotripter at the Singapore general hospital. *Scand J Urol Nephrol*, 2002. 36: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/12487741>
180. Muller-Mattheis, V.G., *et al.* Bacteremia during extracorporeal shock wave lithotripsy of renal calculi. *J Urol*, 1991. 146: 733.
<https://www.ncbi.nlm.nih.gov/pubmed/1875482>
181. Dhar, N.B., *et al.* A multivariate analysis of risk factors associated with subcapsular hematoma formation following electromagnetic shock wave lithotripsy. *J Urol*, 2004. 172: 2271.
<https://www.ncbi.nlm.nih.gov/pubmed/15538247>
182. Zanetti, G., *et al.* Cardiac dysrhythmias induced by extracorporeal shockwave lithotripsy. *J Endourol*, 1999. 13: 409.
<https://www.ncbi.nlm.nih.gov/pubmed/10479005>
183. Rodrigues Netto, N., Jr., *et al.* Small-bowel perforation after shockwave lithotripsy. *J Endourol*, 2003. 17: 719.
<https://www.ncbi.nlm.nih.gov/pubmed/14642028>

184. Holmberg, G., *et al.* Perforation of the bowel during SWL in prone position. *J Endourol*, 1997. 11: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/9355944>
185. Maker, V., *et al.* Gastrointestinal injury secondary to extracorporeal shock wave lithotripsy: a review of the literature since its inception. *J Am Coll Surg*, 2004. 198: 128.
<https://www.ncbi.nlm.nih.gov/pubmed/14698320>
186. Kim, T.B., *et al.* Life-threatening complication after extracorporeal shock wave lithotripsy for a renal stone: a hepatic subcapsular hematoma. *Korean J Urol*, 2010. 51: 212.
<https://www.ncbi.nlm.nih.gov/pubmed/20414400>
187. Ng, C.F., *et al.* Hepatic haematoma after shockwave lithotripsy for renal stones. *Urol Res*, 2012. 40: 785.
<https://www.ncbi.nlm.nih.gov/pubmed/22782117>
188. Chen, C.S., *et al.* Subcapsular hematoma of spleen--a complication following extracorporeal shock wave lithotripsy for ureteral calculus. *Changgeng Yi Xue Za Zhi*, 1992. 15: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/1295657>
189. Preminger, G.M., *et al.* 2007 guideline for the management of ureteral calculi. *J Urol*, 2007. 178: 2418.
<https://www.ncbi.nlm.nih.gov/pubmed/17993340>
190. Lingeman, J.E., *et al.* Blood pressure changes following extracorporeal shock wave lithotripsy and other forms of treatment for nephrolithiasis. *JAMA*, 1990. 263: 1789.
<https://www.ncbi.nlm.nih.gov/pubmed/2313851>
191. Krambeck, A.E., *et al.* Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteral stones at 19 years of followup. *J Urol*, 2006. 175: 1742.
<https://www.ncbi.nlm.nih.gov/pubmed/16600747>
192. Eassa, W.A., *et al.* Prospective study of the long-term effects of shock wave lithotripsy on renal function and blood pressure. *J Urol*, 2008. 179: 9 18207167 64.
<https://www.ncbi.nlm.nih.gov/pubmed/24162890>
193. Yu, C., *et al.* A systematic review and meta-analysis of new onset hypertension after extracorporeal shock wave lithotripsy. *Int Urol Nephrol*, 2014. 46: 719.
<https://www.ncbi.nlm.nih.gov/pubmed/24162890>
194. Fankhauser, C.D., *et al.* Long-term Adverse Effects of Extracorporeal Shock-wave Lithotripsy for Nephrolithiasis and Ureterolithiasis: A Systematic Review. *Urology*, 2015. 85: 991.
<https://www.ncbi.nlm.nih.gov/pubmed/25917723>
195. Lu, Y., *et al.* Randomized prospective trial of tubeless versus conventional minimally invasive percutaneous nephrolithotomy. *World J Urol*, 2013. 31: 1303.
<https://www.ncbi.nlm.nih.gov/pubmed/22903789>
196. Sabnis, R.B., *et al.* Micropercutaneous nephrolithotomy (microperc) vs retrograde intrarenal surgery for the management of small renal calculi: a randomized controlled trial. *BJU Int*, 2013. 112: 355.
<https://www.ncbi.nlm.nih.gov/pubmed/23826843>
197. Yamaguchi, A., *et al.* Operating times and bleeding complications in percutaneous nephrolithotomy: a comparison of tract dilation methods in 5,537 patients in the Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study. *J Endourol*, 2011. 25: 933.
<https://www.ncbi.nlm.nih.gov/pubmed/21568697>
198. Tepeler, A., *et al.* Comparison of intrarenal pelvic pressure during micro-percutaneous nephrolithotomy and conventional percutaneous nephrolithotomy. *Urolithiasis*, 2014. 42: 275.
<https://www.ncbi.nlm.nih.gov/pubmed/Tepeler>
199. Ganesamoni, R., *et al.* Prospective randomized controlled trial comparing laser lithotripsy with pneumatic lithotripsy in miniperc for renal calculi. *J Endourol*, 2013. 27: 1444.
<https://www.ncbi.nlm.nih.gov/pubmed/24251428>
200. Gupta, P.K. Is the holmium:YAG laser the best intracorporeal lithotripter for the ureter? A 3-year retrospective study. *J Endourol*, 2007. 21: 305.
<https://www.ncbi.nlm.nih.gov/pubmed/17444776>
201. Andonian, S., *et al.* Does imaging modality used for percutaneous renal access make a difference? A matched case analysis. *J Endourol*, 2013. 27: 24.
<https://www.ncbi.nlm.nih.gov/pubmed/22834999>
202. Wang, Y., *et al.* Prone versus modified supine position in percutaneous nephrolithotomy: a prospective randomized study. *Int J Med Sci*, 2013. 10: 1518.
<https://www.ncbi.nlm.nih.gov/pubmed/24046526>

203. Mak, D.K., *et al.* What is better in percutaneous nephrolithotomy - Prone or supine? A systematic review. *Arab J Urol*, 2016. 14: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/27489736>
204. Yuan, D., *et al.* Supine Versus Prone Position in Percutaneous Nephrolithotomy for Kidney Calculi: A Meta-Analysis. *J Endourol*, 2016. 30: 754.
<https://www.ncbi.nlm.nih.gov/pubmed/27072075>
205. Cracco, C.M., *et al.* ECIRS (Endoscopic Combined Intrarenal Surgery) in the Galdakao-modified supine Valdivia position: a new life for percutaneous surgery? *World J Urol*, 2011. 29: 821.
<https://www.ncbi.nlm.nih.gov/pubmed/22057344>
206. Isac, W., *et al.* Endoscopic-guided versus fluoroscopic-guided renal access for percutaneous nephrolithotomy: a comparative analysis. *Urology*, 2013. 81: 251.
<https://www.ncbi.nlm.nih.gov/pubmed/23374772>
207. Falahatkar, S., *et al.* Complete supine PCNL: ultrasound vs. fluoroscopic guided: a randomized clinical trial. *Int Braz J Urol*, 2016. 42: 710.
<https://www.ncbi.nlm.nih.gov/pubmed/27564281>
208. Jessen, J.P., *et al.* Percutaneous nephrolithotomy under combined sonographic/radiologic guided puncture: results of a learning curve using the modified Clavien grading system. *World J Urol*, 2013. 31: 1599.
<https://www.ncbi.nlm.nih.gov/pubmed/23283412>
209. Wang, K., *et al.* Ultrasonographic versus Fluoroscopic Access for Percutaneous Nephrolithotomy: A Meta-Analysis. *Urol Int*, 2015. 95: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/25678305>
210. Osman, M., *et al.* Percutaneous nephrolithotomy with ultrasonography-guided renal access: experience from over 300 cases. *BJU Int*, 2005. 96: 875.
<https://www.ncbi.nlm.nih.gov/pubmed/16153221>
211. Desai, M.R., *et al.* A prospective randomized comparison of type of nephrostomy drainage following percutaneous nephrostolithotomy: large bore versus small bore versus tubeless. *J Urol*, 2004. 172: 565.
<https://www.ncbi.nlm.nih.gov/pubmed/15247731>
212. Cormio, L., *et al.* Exit strategies following percutaneous nephrolithotomy (PCNL): a comparison of surgical outcomes in the Clinical Research Office of the Endourological Society (CROES) PCNL Global Study. *World J Urol*, 2013. 31: 1239.
<https://www.ncbi.nlm.nih.gov/pubmed/22752586>
213. Istanbuluoglu, M.O., *et al.* Effectiveness of totally tubeless percutaneous nephrolithotomy in selected patients: a prospective randomized study. *Int Urol Nephrol*, 2009. 41: 541.
<https://www.ncbi.nlm.nih.gov/pubmed/19165617>
214. Garofalo, M., *et al.* Tubeless procedure reduces hospitalization and pain after percutaneous nephrolithotomy: results of a multivariable analysis. *Urolithiasis*, 2013. 41: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/23632910>
215. Gonen, M., *et al.* Tubeless and stentless percutaneous nephrolithotomy in patients requiring supracostal access. *Urol Int*, 2009. 82: 440.
<https://www.ncbi.nlm.nih.gov/pubmed/19506412>
216. Seitz, C., *et al.* Incidence, prevention, and management of complications following percutaneous nephrolitholapaxy. *Eur Urol*, 2012. 61: 146.
<https://www.ncbi.nlm.nih.gov/pubmed/21978422>
217. Zanetti, G., *et al.* Infections and urolithiasis: current clinical evidence in prophylaxis and antibiotic therapy. *Arch Ital Urol Androl*, 2008. 80: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/18533618>
218. Gonen, M., *et al.* Factors affecting fever following percutaneous nephrolithotomy: a prospective clinical study. *J Endourol*, 2008. 22: 2135.
<https://www.ncbi.nlm.nih.gov/pubmed/18811569>
219. Wendt-Nordahl, G., *et al.* Do new generation flexible ureterorenoscopes offer a higher treatment success than their predecessors? *Urol Res*, 2011. 39: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/21052986>
220. Binbay, M., *et al.* Is there a difference in outcomes between digital and fiberoptic flexible ureterorenoscopy procedures? *J Endourol*, 2010. 24: 1929.
<https://www.ncbi.nlm.nih.gov/pubmed/21043835>
221. Geraghty, R., *et al.* Evidence for Ureterorenoscopy and Laser Fragmentation (URSL) for Large Renal Stones in the Modern Era. *Curr Urol Rep*, 2015. 16: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/26077357>

222. Humphreys, M.R., *et al.* A new world revealed: early experience with digital ureteroscopy. *J Urol*, 2008. 179: 970.
<https://www.ncbi.nlm.nih.gov/pubmed/18207196>
223. Mitchell, S., *et al.* First digital flexible ureterorenoscope: initial experience. *J Endourol*, 2008. 22: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/18315473>
224. Auge, B.K., *et al.* Ureteroscopic management of lower-pole renal calculi: technique of calculus displacement. *J Endourol*, 2001. 15: 835.
<https://www.ncbi.nlm.nih.gov/pubmed/11724125>
225. Assimos, D.G., *et al.* The role of open stone surgery since extracorporeal shock wave lithotripsy. *J Urol*, 1989. 142: 263.
<https://www.ncbi.nlm.nih.gov/pubmed/2746742>
226. Segura, J.W. Current surgical approaches to nephrolithiasis. *Endocrinol Metab Clin North Am*, 1990. 19: 919.
<https://www.ncbi.nlm.nih.gov/pubmed/2081519>
227. Honeck, P., *et al.* Does open stone surgery still play a role in the treatment of urolithiasis? Data of a primary urolithiasis center. *J Endourol*, 2009. 23: 1209.
<https://www.ncbi.nlm.nih.gov/pubmed/19538063>
228. Bichler, K.H., *et al.* Indications for open stone removal of urinary calculi. *Urol Int*, 1997. 59: 102.
<https://www.ncbi.nlm.nih.gov/pubmed/9392057>
229. Paik, M.L., *et al.* Is there a role for open stone surgery? *Urol Clin North Am*, 2000. 27: 323.
<https://www.ncbi.nlm.nih.gov/pubmed/10778474>
230. Ansari, M.S., *et al.* Impact of socioeconomic status in etiology and management of urinary stone disease. *Urol Int*, 2003. 70: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/12776701>
231. Alivizatos, G., *et al.* Is there still a role for open surgery in the management of renal stones? *Curr Opin Urol*, 2006. 16: 106.
<https://www.ncbi.nlm.nih.gov/pubmed/16479213>
232. Basiri, A., *et al.* Comparison of safety and efficacy of laparoscopic pyelolithotomy versus percutaneous nephrolithotomy in patients with renal pelvic stones: a randomized clinical trial. *Urol J*, 2014. 11: 1932.
<https://www.ncbi.nlm.nih.gov/pubmed/25433470>
233. Beltrami, P., *et al.* The endourological treatment of renal matrix stones. *Urol Int*, 2014. 93: 394.
<https://www.ncbi.nlm.nih.gov/pubmed/24969358>
234. Prakash, J., *et al.* Retroperitoneoscopic versus open mini-incision ureterolithotomy for upper- and mid-ureteric stones: a prospective randomized study. *Urolithiasis*, 2014. 42: 133.
<https://www.ncbi.nlm.nih.gov/pubmed/24272062>
235. Al-Hunayan, A., *et al.* Management of solitary renal pelvic stone: laparoscopic retroperitoneal pyelolithotomy versus percutaneous nephrolithotomy. *J Endourol*, 2011. 25: 975.
<https://www.ncbi.nlm.nih.gov/pubmed/21612433>
236. Skolarikos, A., *et al.* Laparoscopic urinary stone surgery: an updated evidence-based review. *Urol Res*, 2010. 38: 337.
<https://www.ncbi.nlm.nih.gov/pubmed/20396871>
237. Giedelman, C., *et al.* Laparoscopic anatomic nephrolithotomy: developments of the technique in the era of minimally invasive surgery. *J Endourol*, 2012. 26: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/22142215>
238. Wang, X., *et al.* Laparoscopic pyelolithotomy compared to percutaneous nephrolithotomy as surgical management for large renal pelvic calculi: a meta-analysis. *J Urol*, 2013. 190: 888.
<https://www.ncbi.nlm.nih.gov/pubmed/23454154>
239. Singh, V., *et al.* Prospective randomized comparison of retroperitoneoscopic pyelolithotomy versus percutaneous nephrolithotomy for solitary large pelvic kidney stones. *Urol Int*, 2014. 92: 392.
<https://www.ncbi.nlm.nih.gov/pubmed/24135482>
240. Brandt, B., *et al.* Painful caliceal calculi. The treatment of small nonobstructing caliceal calculi in patients with symptoms. *Scand J Urol Nephrol*, 1993. 27: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/8493473>
241. Burgher, A., *et al.* Progression of nephrolithiasis: long-term outcomes with observation of asymptomatic calculi. *J Endourol*, 2004. 18: 534.
<https://www.ncbi.nlm.nih.gov/pubmed/15333216>
242. Hubner, W., *et al.* Treatment of caliceal calculi. *Br J Urol*, 1990. 66: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/2393803>

243. Keeley, F.X., Jr., *et al.* Preliminary results of a randomized controlled trial of prophylactic shock wave lithotripsy for small asymptomatic renal calyceal stones. *BJU Int*, 2001. 87: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/11121982>
244. Glowacki, L.S., *et al.* The natural history of asymptomatic urolithiasis. *J Urol*, 1992. 147: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/1732583>
245. Collins, J.W., *et al.* Is there a role for prophylactic shock wave lithotripsy for asymptomatic calyceal stones? *Curr Opin Urol*, 2002. 12: 281.
<https://www.ncbi.nlm.nih.gov/pubmed/12072647>
246. Rebuck, D.A., *et al.* The natural history of renal stone fragments following ureteroscopy. *Urology*, 2011. 77: 564.
<https://www.ncbi.nlm.nih.gov/pubmed/21109293>
247. Andersson, L., *et al.* Small renal caliceal calculi as a cause of pain. *J Urol*, 1983. 130: 752.
<https://www.ncbi.nlm.nih.gov/pubmed/6887409>
248. Mee, S.L., *et al.* Small caliceal stones: is extracorporeal shock wave lithotripsy justified? *J Urol*, 1988. 139: 908.
<https://www.ncbi.nlm.nih.gov/pubmed/3361660>
249. Argyropoulos, A.N., *et al.* Evaluation of outcome following lithotripsy. *Curr Opin Urol*, 2010. 20: 154.
<https://www.ncbi.nlm.nih.gov/pubmed/19898239>
250. Srisubat, A., *et al.* Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones. *Cochrane Database Syst Rev*, 2014. 11: CD007044.
<https://www.ncbi.nlm.nih.gov/pubmed/25418417>
251. Sahinkanat, T., *et al.* Evaluation of the effects of relationships between main spatial lower pole calyceal anatomic factors on the success of shock-wave lithotripsy in patients with lower pole kidney stones. *Urology*, 2008. 71: 801.
<https://www.ncbi.nlm.nih.gov/pubmed/18279941>
252. Danuser, H., *et al.* Extracorporeal shock wave lithotripsy of lower calyx calculi: how much is treatment outcome influenced by the anatomy of the collecting system? *Eur Urol*, 2007. 52: 539.
<https://www.ncbi.nlm.nih.gov/pubmed/17400366>
253. Preminger, G.M. Management of lower pole renal calculi: shock wave lithotripsy versus percutaneous nephrolithotomy versus flexible ureteroscopy. *Urol Res*, 2006. 34: 108.
<https://www.ncbi.nlm.nih.gov/pubmed/16463145>
254. Zheng, C., *et al.* Extracorporeal shock wave lithotripsy versus retrograde intrarenal surgery for treatment for renal stones 1-2 cm: a meta-analysis. *Urolithiasis*, 2015. 43: 549.
<https://www.ncbi.nlm.nih.gov/pubmed/26211003>
255. Zheng, C., *et al.* Retrograde intrarenal surgery versus percutaneous nephrolithotomy for treatment of renal stones >2 cm: a meta-analysis. *Urol Int*, 2014. 93: 417.
<https://www.ncbi.nlm.nih.gov/pubmed/25170589>
256. Karakoyunlu, N., *et al.* A comparison of standard PCNL and staged retrograde FURS in pelvis stones over 2 cm in diameter: a prospective randomized study. *Urolithiasis*, 2015. 43: 283.
<https://www.ncbi.nlm.nih.gov/pubmed/25295266>
257. Donaldson, J.F., *et al.* Systematic review and meta-analysis of the clinical effectiveness of shock wave lithotripsy, retrograde intrarenal surgery, and percutaneous nephrolithotomy for lower-pole renal stones. *Eur Urol*, 2015. 67: 612.
<https://www.ncbi.nlm.nih.gov/pubmed/25449204>
258. Kumar, A., *et al.* A prospective, randomized comparison of shock wave lithotripsy, retrograde intrarenal surgery and miniperc for treatment of 1 to 2 cm radiolucent lower calyceal renal calculi: a single center experience. *J Urol*, 2015. 193: 160.
<https://www.ncbi.nlm.nih.gov/pubmed/25177768>
259. Sener, N.C., *et al.* Prospective randomized trial comparing shock wave lithotripsy and flexible ureterorenoscopy for lower pole stones smaller than 1 cm. *Urolithiasis*, 2014. 42: 127.
<https://www.ncbi.nlm.nih.gov/pubmed/24220692>
260. Manikandan, R., *et al.* Do anatomic factors pose a significant risk in the formation of lower pole stones? *Urology*, 2007. 69: 620.
<https://www.ncbi.nlm.nih.gov/pubmed/17445636>
261. De, S., *et al.* Percutaneous nephrolithotomy versus retrograde intrarenal surgery: a systematic review and meta-analysis. *Eur Urol*, 2015. 67: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/25064687>

262. Sener, N.C., *et al.* Asymptomatic lower pole small renal stones: shock wave lithotripsy, flexible ureteroscopy, or observation? A prospective randomized trial. *Urology*, 2015. 85: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/25440816>
263. Kumar, A., *et al.* A Prospective Randomized Comparison Between Shock Wave Lithotripsy and Flexible Ureterorenoscopy for Lower Caliceal Stones ≤ 2 cm: A Single-Center Experience. *J Endourol*, 2015. 29: 575.
<https://www.ncbi.nlm.nih.gov/pubmed/25203489>
264. Mi, Y., *et al.* Flexible ureterorenoscopy (F-URS) with holmium laser versus extracorporeal shock wave lithotripsy (ESWL) for treatment of renal stone < 2 cm: a meta-analysis. *Urolithiasis*, 2016. 44: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/26530230>
265. Zhang, W., *et al.* Retrograde Intrarenal Surgery Versus Percutaneous Nephrolithotomy Versus Extracorporeal Shockwave Lithotripsy for Treatment of Lower Pole Renal Stones: A Meta-Analysis and Systematic Review. *J Endourol*, 2015. 29: 745.
<https://www.ncbi.nlm.nih.gov/pubmed/25531986>
266. Sumino, Y., *et al.* Predictors of lower pole renal stone clearance after extracorporeal shock wave lithotripsy. *J Urol*, 2002. 168: 1344.
<https://www.ncbi.nlm.nih.gov/pubmed/12352389>
267. Torricelli, F.C., *et al.* Impact of renal anatomy on shock wave lithotripsy outcomes for lower pole kidney stones: results of a prospective multifactorial analysis controlled by computerized tomography. *J Urol*, 2015. 193: 2002.
<https://www.ncbi.nlm.nih.gov/pubmed/25524240>
268. Gupta, N.P., *et al.* Infundibulopelvic anatomy and clearance of inferior caliceal calculi with shock wave lithotripsy. *J Urol*, 2000. 163: 24.
<https://www.ncbi.nlm.nih.gov/pubmed/10604306>
269. Abdelhamid, M., *et al.* A Prospective Evaluation of High-Resolution CT Parameters in Predicting Extracorporeal Shockwave Lithotripsy Success for Upper Urinary Tract Calculi. *J Endourol*, 2016. 30: 1227.
<https://www.ncbi.nlm.nih.gov/pubmed/27597174>
270. Chiong, E., *et al.* Randomized controlled study of mechanical percussion, diuresis, and inversion therapy to assist passage of lower pole renal calculi after shock wave lithotripsy. *Urology*, 2005. 65: 1070.
<https://www.ncbi.nlm.nih.gov/pubmed/15922429>
271. Madbouly, K., *et al.* Impact of lower pole renal anatomy on stone clearance after shock wave lithotripsy: fact or fiction? *J Urol*, 2001. 165: 1415.
<https://www.ncbi.nlm.nih.gov/pubmed/11342888>
272. Hyams, E.S., *et al.* Flexible ureterorenoscopy and holmium laser lithotripsy for the management of renal stone burdens that measure 2 to 3 cm: a multi-institutional experience. *J Endourol*, 2010. 24: 1583.
<https://www.ncbi.nlm.nih.gov/pubmed/20629566>
273. Riley, J.M., *et al.* Retrograde ureteroscopy for renal stones larger than 2.5 cm. *J Endourol*, 2009. 23: 1395.
<https://www.ncbi.nlm.nih.gov/pubmed/19694527>
274. Akman, T., *et al.* Comparison of percutaneous nephrolithotomy and retrograde flexible nephrolithotripsy for the management of 2-4 cm stones: a matched-pair analysis. *BJU Int*, 2012. 109: 1384.
<https://www.ncbi.nlm.nih.gov/pubmed/22093679>
275. Skolarikos, A., *et al.* The role for active monitoring in urinary stones: a systematic review. *J Endourol*, 2010. 24: 923.
<https://www.ncbi.nlm.nih.gov/pubmed/20482232>
276. Dellabella, M., *et al.* Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol*, 2005. 174: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/15947613>
277. Borghi, L., *et al.* Nifedipine and methylprednisolone in facilitating ureteral stone passage: a randomized, double-blind, placebo-controlled study. *J Urol*, 1994. 152: 1095.
<https://www.ncbi.nlm.nih.gov/pubmed/8072071>
278. Porpiglia, F., *et al.* Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. *Urology*, 2000. 56: 579.
<https://www.ncbi.nlm.nih.gov/pubmed/11018608>

279. Dellabella, M., *et al.* Medical-expulsive therapy for distal ureterolithiasis: randomized prospective study on role of corticosteroids used in combination with tamsulosin-simplified treatment regimen and health-related quality of life. *Urology*, 2005. 66: 712.
<https://www.ncbi.nlm.nih.gov/pubmed/16230122>
280. Campschroer, T., *et al.* Alpha-blockers as medical expulsive therapy for ureteral stones. *Cochrane Database Syst Rev*, 2014. 4: CD008509.
<https://www.ncbi.nlm.nih.gov/pubmed/24691989>
281. Sur, R.L., *et al.* Silodosin to facilitate passage of ureteral stones: a multi-institutional, randomized, double-blinded, placebo-controlled trial. *Eur Urol*, 2015. 67: 959.
<https://www.ncbi.nlm.nih.gov/pubmed/25465978>
282. Turk, C., *et al.* Medical Expulsive Therapy for Ureterolithiasis: The EAU Recommendations in 2016. *Eur Urol*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27506951>
283. Porphiglia, F., *et al.* Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: single drug or association? *Eur Urol*, 2006. 50: 339.
<https://www.ncbi.nlm.nih.gov/pubmed/16574310>
284. Yilmaz, E., *et al.* The comparison and efficacy of 3 different alpha1-adrenergic blockers for distal ureteral stones. *J Urol*, 2005. 173: 2010.
<https://www.ncbi.nlm.nih.gov/pubmed/15879806>
285. Ghoneim, I.A., *et al.* Extracorporeal shock wave lithotripsy in impacted upper ureteral stones: a prospective randomized comparison between stented and non-stented techniques. *Urology*, 2010. 75: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/19811806>
286. Cybulski, P.A., *et al.* Ureteroscopy: anesthetic considerations. *Urol Clin North Am*, 2004. 31: 43.
<https://www.ncbi.nlm.nih.gov/pubmed/15040400>
287. Sun, X., *et al.* Treatment of large impacted proximal ureteral stones: randomized comparison of percutaneous antegrade ureterolithotripsy versus retrograde ureterolithotripsy. *J Endourol*, 2008. 22: 913.
<https://www.ncbi.nlm.nih.gov/pubmed/18429682>
288. Dickstein, R.J., *et al.* Is a safety wire necessary during routine flexible ureteroscopy? *J Endourol*, 2010. 24: 1589.
<https://www.ncbi.nlm.nih.gov/pubmed/20836719>
289. Eandi, J.A., *et al.* Evaluation of the impact and need for use of a safety guidewire during ureteroscopy. *J Endourol*, 2008. 22: 1653.
<https://www.ncbi.nlm.nih.gov/pubmed/18721045>
290. Ulvik, O., *et al.* Ureteroscopy with and without safety guide wire: should the safety wire still be mandatory? *J Endourol*, 2013. 27: 1197.
<https://www.ncbi.nlm.nih.gov/pubmed/23795760>
291. Ge, H., *et al.* Bilateral Same-Session Ureteroscopy for Treatment of Ureteral Calculi: A Systematic Review and Meta-Analysis. *J Endourol*, 2016. 30: 1169.
<https://www.ncbi.nlm.nih.gov/pubmed/27626367>
292. Stern, J.M., *et al.* Safety and efficacy of ureteral access sheaths. *J Endourol*, 2007. 21: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/17338606>
293. L'Esperance J, O., *et al.* Effect of ureteral access sheath on stone-free rates in patients undergoing ureteroscopic management of renal calculi. *Urology*, 2005. 66: 252.
<https://www.ncbi.nlm.nih.gov/pubmed/16040093>
294. Traxer, O., *et al.* Prospective evaluation and classification of ureteral wall injuries resulting from insertion of a ureteral access sheath during retrograde intrarenal surgery. *J Urol*, 2013. 189: 580.
<https://www.ncbi.nlm.nih.gov/pubmed/22982421>
295. Aboumarzouk, O.M., *et al.* Flexible ureteroscopy and laser lithotripsy for stones >2 cm: a systematic review and meta-analysis. *J Endourol*, 2012. 26: 1257.
<https://www.ncbi.nlm.nih.gov/pubmed/22642568>
296. Bach, T., *et al.* Working tools in flexible ureterorenoscopy--influence on flow and deflection: what does matter? *J Endourol*, 2008. 22: 1639.
<https://www.ncbi.nlm.nih.gov/pubmed/18620506>
297. Leijte, J.A., *et al.* Holmium laser lithotripsy for ureteral calculi: predictive factors for complications and success. *J Endourol*, 2008. 22: 257.
<https://www.ncbi.nlm.nih.gov/pubmed/18294030>
298. Pierre, S., *et al.* Holmium laser for stone management. *World J Urol*, 2007. 25: 235.
<https://www.ncbi.nlm.nih.gov/pubmed/17340157>

299. Garg, S., *et al.* Ureteroscopic laser lithotripsy versus ballistic lithotripsy for treatment of ureteric stones: a prospective comparative study. *Urol Int*, 2009. 82: 341.
<https://www.ncbi.nlm.nih.gov/pubmed/19440025>
300. Binbay, M., *et al.* Evaluation of pneumatic versus holmium:YAG laser lithotripsy for impacted ureteral stones. *Int Urol Nephrol*, 2011. 43: 989.
<https://www.ncbi.nlm.nih.gov/pubmed/21479563>
301. Ahmed, M., *et al.* Systematic evaluation of ureteral occlusion devices: insertion, deployment, stone migration, and extraction. *Urology*, 2009. 73: 976.
<https://www.ncbi.nlm.nih.gov/pubmed/19394493>
302. John, T.T., *et al.* Adjunctive tamsulosin improves stone free rate after ureteroscopic lithotripsy of large renal and ureteric calculi: a prospective randomized study. *Urology*, 2010. 75: 1040.
<https://www.ncbi.nlm.nih.gov/pubmed/19819530>
303. Assimos, D., *et al.* Preoperative JJ stent placement in ureteric and renal stone treatment: results from the Clinical Research Office of Endourological Society (CROES) ureteroscopy (URS) Global Study. *BJU Int*, 2016. 117: 648.
<https://www.ncbi.nlm.nih.gov/pubmed/26237735>
304. Jessen, J.P., *et al.* International Collaboration in Endourology: Multicenter Evaluation of Prestenting for Ureterorenoscopy. *J Endourol*, 2016. 30: 268.
<https://www.ncbi.nlm.nih.gov/pubmed/26582170>
305. Song, T., *et al.* Meta-analysis of postoperatively stenting or not in patients underwent ureteroscopic lithotripsy. *Urol Res*, 2012. 40: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/21573923>
306. Haleblan, G., *et al.* Ureteral stenting and urinary stone management: a systematic review. *J Urol*, 2008. 179: 424.
<https://www.ncbi.nlm.nih.gov/pubmed/18076928>
307. Nabi, G., *et al.* Outcomes of stenting after uncomplicated ureteroscopy: systematic review and meta-analysis. *BMJ*, 2007. 334: 572.
<https://www.ncbi.nlm.nih.gov/pubmed/17311851>
308. Moon, T.D. Ureteral stenting--an obsolete procedure? *J Urol*, 2002. 167: 1984.
<https://www.ncbi.nlm.nih.gov/pubmed/11956423>
309. Wang, C.J., *et al.* Effects of specific alpha-1A/1D blocker on lower urinary tract symptoms due to double-J stent: a prospectively randomized study. *Urol Res*, 2009. 37: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/19277623>
310. Lee, Y.J., *et al.* Solifenacin improves double-J stent-related symptoms in both genders following uncomplicated ureteroscopic lithotripsy. *Urolithiasis*, 2013. 41: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/23515684>
311. Lamb, A.D., *et al.* Meta-analysis showing the beneficial effect of alpha-blockers on ureteric stent discomfort. *BJU Int*, 2011. 108: 1894.
<https://www.ncbi.nlm.nih.gov/pubmed/21453351>
312. Geavlete, P., *et al.* Complications of 2735 retrograde semirigid ureteroscopy procedures: a single-center experience. *J Endourol*, 2006. 20: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/16548724>
313. Perez Castro, E., *et al.* Differences in ureteroscopic stone treatment and outcomes for distal, mid-, proximal, or multiple ureteral locations: the Clinical Research Office of the Endourological Society ureteroscopy global study. *Eur Urol*, 2014. 66: 102.
<https://www.ncbi.nlm.nih.gov/pubmed/24507782>
314. Kumar, V., *et al.* Percutaneous ureterolitholapaxy: the best bet to clear large bulk impacted upper ureteral calculi. *Arch Esp Urol*, 1996. 49: 86.
<https://www.ncbi.nlm.nih.gov/pubmed/8678608>
315. el-Nahas, A.R., *et al.* Percutaneous treatment of large upper tract stones after urinary diversion. *Urology*, 2006. 68: 500.
<https://www.ncbi.nlm.nih.gov/pubmed/16979745>
316. El-Assmy, A., *et al.* Extracorporeal shock wave lithotripsy of upper urinary tract calculi in patients with cystectomy and urinary diversion. *Urology*, 2005. 66: 510.
<https://www.ncbi.nlm.nih.gov/pubmed/16140067>
317. Moufid, K., *et al.* Large impacted upper ureteral calculi: A comparative study between retrograde ureterolithotripsy and percutaneous antegrade ureterolithotripsy in the modified lateral position. *Urol Ann*, 2013. 5: 140.
<https://www.ncbi.nlm.nih.gov/pubmed/24049373>

318. Topaloglu, H., *et al.* A comparison of antegrade percutaneous and laparoscopic approaches in the treatment of proximal ureteral stones. *Biomed Res Int*, 2014. 2014: 691946.
<https://www.ncbi.nlm.nih.gov/pubmed/25295266>
319. Kumar, A., *et al.* A Prospective Randomized Comparison Between Laparoscopic Ureterolithotomy and Semirigid Ureteroscopy for Upper Ureteral Stones >2 cm: A Single-Center Experience. *J Endourol*, 2015. 29: 1248.
<https://www.ncbi.nlm.nih.gov/pubmed/25177768>
320. Torricelli, F.C., *et al.* Semi-rigid ureteroscopic lithotripsy versus laparoscopic ureterolithotomy for large upper ureteral stones: a meta - analysis of randomized controlled trials. *Int Braz J Urol*, 2016. 42: 645.
<https://www.ncbi.nlm.nih.gov/pubmed/27564273>
321. Skolarikos, A., *et al.* Indications, prediction of success and methods to improve outcome of shock wave lithotripsy of renal and upper ureteral calculi. *Arch Ital Urol Androl*, 2010. 82: 56.
<https://www.ncbi.nlm.nih.gov/pubmed/20593724>
322. Cui, X., *et al.* Comparison between extracorporeal shock wave lithotripsy and ureteroscopic lithotripsy for treating large proximal ureteral stones: a meta-analysis. *Urology*, 2015. 85: 748.
<https://www.ncbi.nlm.nih.gov/pubmed/25681251>
323. Ishii, H., *et al.* Outcomes of Systematic Review of Ureteroscopy for Stone Disease in the Obese and Morbidly Obese Population. *J Endourol*, 2016. 30: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/26415049>
324. El-Nahas, A.R., *et al.* Predictors of clinical significance of residual fragments after extracorporeal shockwave lithotripsy for renal stones. *J Endourol*, 2006. 20: 870.
<https://www.ncbi.nlm.nih.gov/pubmed/17144853>
325. Buchholz, N.P., *et al.* Minor residual fragments after extracorporeal shockwave lithotripsy: spontaneous clearance or risk factor for recurrent stone formation? *J Endourol*, 1997. 11: 227.
<https://www.ncbi.nlm.nih.gov/pubmed/9376838>
326. Beck, E.M., *et al.* The fate of residual fragments after extracorporeal shock wave lithotripsy monotherapy of infection stones. *J Urol*, 1991. 145: 6.
<https://www.ncbi.nlm.nih.gov/pubmed/1984100>
327. Candau, C., *et al.* Natural history of residual renal stone fragments after ESWL. *Eur Urol*, 2000. 37: 18.
<https://www.ncbi.nlm.nih.gov/pubmed/10671779>
328. Chew, B.H., *et al.* Natural History, Complications and Re-Intervention Rates of Asymptomatic Residual Stone Fragments after Ureteroscopy: a Report from the EDGE Research Consortium. *J Urol*, 2016. 195: 982.
<https://www.ncbi.nlm.nih.gov/pubmed/26585680>
329. Krings, F., *et al.* Extracorporeal shock wave lithotripsy retreatment ("stir-up") promotes discharge of persistent caliceal stone fragments after primary extracorporeal shock wave lithotripsy. *J Urol*, 1992. 148: 1040.
<https://www.ncbi.nlm.nih.gov/pubmed/1507326>
330. Fine, J.K., *et al.* Effect of medical management and residual fragments on recurrent stone formation following shock wave lithotripsy. *J Urol*, 1995. 153: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/7966783>
331. Siener, R., *et al.* Prospective study on the efficacy of a selective treatment and risk factors for relapse in recurrent calcium oxalate stone patients. *Eur Urol*, 2003. 44: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/14499683>
332. Cicerello, E., *et al.* Effect of alkaline citrate therapy on clearance of residual renal stone fragments after extracorporeal shock wave lithotripsy in sterile calcium and infection nephrolithiasis patients. *J Urol*, 1994. 151: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/8254832>
333. Tsai, Y.L., *et al.* Comparative study of conservative and surgical management for symptomatic moderate and severe hydronephrosis in pregnancy: a prospective randomized study. *Acta Obstet Gynecol Scand*, 2007. 86: 1047.
<https://www.ncbi.nlm.nih.gov/pubmed/17712643>
334. Mokhmalji, H., *et al.* Percutaneous nephrostomy versus ureteral stents for diversion of hydronephrosis caused by stones: a prospective, randomized clinical trial. *J Urol*, 2001. 165: 1088.
<https://www.ncbi.nlm.nih.gov/pubmed/11257644>
335. vanSonnenberg, E., *et al.* Symptomatic renal obstruction or urosepsis during pregnancy: treatment by sonographically guided percutaneous nephrostomy. *AJR Am J Roentgenol*, 1992. 158: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/1727366>

336. Semins, M.J., *et al.* The safety of ureteroscopy during pregnancy: a systematic review and meta-analysis. *J Urol*, 2009. 181: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/19012926>
337. Ishii, H., *et al.* Current status of ureteroscopy for stone disease in pregnancy. *Urolithiasis*, 2014. 42: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/24374899>
338. Teleb, M., *et al.* Definitive ureteroscopy and intracorporeal lithotripsy in treatment of ureteral calculi during pregnancy. *Arab J Urol*, 2014. 12: 299.
<https://www.ncbi.nlm.nih.gov/pubmed/26019966>
339. Toth, C., *et al.* Percutaneous nephrolithotomy in early pregnancy. *Int Urol Nephrol*, 2005. 37: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/16132747>
340. Kato, H., *et al.* Continent urinary reservoir formation with transverse colon for patients with pelvic irradiation. *Int J Urol*, 2002. 9: 200.
<https://www.ncbi.nlm.nih.gov/pubmed/12010313>
341. Holmes, D.G., *et al.* Long-term complications related to the modified Indiana pouch. *Urology*, 2002. 60: 603.
<https://www.ncbi.nlm.nih.gov/pubmed/12385916>
342. Yang, W.J., *et al.* Long-term effects of ileal conduit urinary diversion on upper urinary tract in bladder cancer. *Urology*, 2006. 68: 324.
<https://www.ncbi.nlm.nih.gov/pubmed/16904445>
343. Assimos, D.G. Nephrolithiasis in patients with urinary diversion. *J Urol*, 1996. 155: 69.
<https://www.ncbi.nlm.nih.gov/pubmed/7490901>
344. Cohen, T.D., *et al.* Long-term incidence and risks for recurrent stones following contemporary management of upper tract calculi in patients with a urinary diversion. *J Urol*, 1996. 155: 62.
<https://www.ncbi.nlm.nih.gov/pubmed/7490899>
345. Deliveliotis, C., *et al.* Shockwave lithotripsy for urinary stones in patients with urinary diversion after radical cystectomy. *J Endourol*, 2002. 16: 717.
<https://www.ncbi.nlm.nih.gov/pubmed/12542873>
346. Stein, J.P., *et al.* Complications of the afferent antireflux valve mechanism in the Kock ileal reservoir. *J Urol*, 1996. 155: 1579.
<https://www.ncbi.nlm.nih.gov/pubmed/8627827>
347. Matlaga, B.R., *et al.* Computerized tomography guided access for percutaneous nephrostolithotomy. *J Urol*, 2003. 170: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/12796641>
348. Hensle, T.W., *et al.* Preventing reservoir calculi after augmentation cystoplasty and continent urinary diversion: the influence of an irrigation protocol. *BJU Int*, 2004. 93: 585.
<https://www.ncbi.nlm.nih.gov/pubmed/15008735>
349. Raj, G.V., *et al.* The incidence of nephrolithiasis in patients with spinal neural tube defects. *J Urol*, 1999. 162: 1238.
<https://www.ncbi.nlm.nih.gov/pubmed/10458475>
350. Gros, D.A., *et al.* Urolithiasis in spina bifida. *Eur J Pediatr Surg*, 1998. 8 Suppl 1: 68.
<https://www.ncbi.nlm.nih.gov/pubmed/9926338>
351. Kondo, A., *et al.* [Urolithiasis in those patients with myelodysplasia]. *Nihon Hinyokika Gakkai Zasshi*, 2003. 94: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/12638200>
352. Rendeli, C., *et al.* Latex sensitisation and allergy in children with myelomeningocele. *Childs Nerv Syst*, 2006. 22: 28.
<https://www.ncbi.nlm.nih.gov/pubmed/15703967>
353. Christman, M.S., *et al.* Morbidity and efficacy of ureteroscopic stone treatment in patients with neurogenic bladder. *J Urol*, 2013. 190: 1479.
<https://www.ncbi.nlm.nih.gov/pubmed/23454151>
354. Harper, J.M., *et al.* Risk factors for calculus formation in patients with renal transplants. *Br J Urol*, 1994. 74: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/7921929>
355. Cho, D.K., *et al.* Urinary calculi in renal transplant recipients. *Transplantation*, 1988. 45: 899.
<https://www.ncbi.nlm.nih.gov/pubmed/3285534>
356. Hayes, J.M., *et al.* Renal transplant calculi. A reevaluation of risks and management. *Transplantation*, 1989. 47: 949.
<https://www.ncbi.nlm.nih.gov/pubmed/2660356>

357. Shoskes, D.A., *et al.* Urological complications in 1,000 consecutive renal transplant recipients. *J Urol*, 1995. 153: 18.
<https://www.ncbi.nlm.nih.gov/pubmed/7966766>
358. Klingler, H.C., *et al.* Urolithiasis in allograft kidneys. *Urology*, 2002. 59: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/11880067>
359. Trivedi, A., *et al.* Management of calculi in a donor kidney. *Transplant Proc*, 2007. 39: 761.
<https://www.ncbi.nlm.nih.gov/pubmed/17445593>
360. Yigit, B., *et al.* Stone disease in kidney transplantation. *Transplant Proc*, 2004. 36: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/15013342>
361. Gupta, M., *et al.* Treatment of stones associated with complex or anomalous renal anatomy. *Urol Clin North Am*, 2007. 34: 431.
<https://www.ncbi.nlm.nih.gov/pubmed/17678992>
362. Challacombe, B., *et al.* Multimodal management of urolithiasis in renal transplantation. *BJU Int*, 2005. 96: 385.
<https://www.ncbi.nlm.nih.gov/pubmed/16042735>
363. Rifaioglu, M.M., *et al.* Percutaneous management of stones in transplanted kidneys. *Urology*, 2008. 72: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/18653217>
364. Minon Cifuentes, J., *et al.* Percutaneous nephrolithotomy in transplanted kidney. *Urology*, 1991. 38: 232.
<https://www.ncbi.nlm.nih.gov/pubmed/1887537>
365. Wyatt, J., *et al.* Treatment outcomes for percutaneous nephrolithotomy in renal allografts. *J Endourol*, 2009. 23: 1821.
<https://www.ncbi.nlm.nih.gov/pubmed/19814697>
366. Del Pizzo, J.J., *et al.* Ureteroscopic evaluation in renal transplant recipients. *J Endourol*, 1998. 12: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/9607439>
367. Basiri, A., *et al.* Ureteroscopic management of urological complications after renal transplantation. *Scand J Urol Nephrol*, 2006. 40: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/16452057>
368. Lu, H.F., *et al.* Donor-gifted allograft urolithiasis: early percutaneous management. *Urology*, 2002. 59: 25.
<https://www.ncbi.nlm.nih.gov/pubmed/11796274>
369. Rhoderick, T.M., *et al.* Extracorporeal shock wave lithotripsy in the renal transplant patient: a case report and review of literature. *Clin Transplant*, 1992. 6: 375.
<https://www.ncbi.nlm.nih.gov/pubmed/10147926>
370. Atala, A., *et al.* Extracorporeal shock-wave lithotripsy in transplanted kidney. *Urology*, 1993. 41: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/8420082>
371. Raboy, A., *et al.* Laparoscopic ureterolithotomy. *Urology*, 1992. 39: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/1532102>
372. Gaur, D.D. Retroperitoneal endoscopic ureterolithotomy: our experience in 12 patients. *J Endourol*, 1993. 7: 501.
<https://www.ncbi.nlm.nih.gov/pubmed/8124346>
373. Gaur, D.D. Retroperitoneal laparoscopic ureterolithotomy. *World J Urol*, 1993. 11: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/8401638>
374. Gaur, D.D., *et al.* Retroperitoneal laparoscopic pyelolithotomy. *J Urol*, 1994. 151: 927.
<https://www.ncbi.nlm.nih.gov/pubmed/8126827>
375. Escovar Diaz, P., *et al.* [Laparoscopic ureterolithotomy]. *Arch Esp Urol*, 1993. 46: 633.
<https://www.ncbi.nlm.nih.gov/pubmed/8239742>
376. Locke, D.R., *et al.* Extracorporeal shock-wave lithotripsy in horseshoe kidneys. *Urology*, 1990. 35: 407.
<https://www.ncbi.nlm.nih.gov/pubmed/2336770>
377. Somani, B.K., *et al.* E33 Outcome of ureteroscopy for stone disease in patients with horseshoe kidney (HSK): Results from a systematic review of literature. *Eur Urol Suppl*. 12: 41. [No abstract available].
378. Gelet, A., *et al.* Endopyelotomy with the Acucise cutting balloon device. Early clinical experience. *Eur Urol*, 1997. 31: 389.
<https://www.ncbi.nlm.nih.gov/pubmed/9187895>

379. Faerber, G.J., *et al.* Retrograde treatment of ureteropelvic junction obstruction using the ureteral cutting balloon catheter. *J Urol*, 1997. 157: 454.
<https://www.ncbi.nlm.nih.gov/pubmed/8996330>
380. Berkman, D.S., *et al.* Treatment outcomes after endopyelotomy performed with or without simultaneous nephrolithotomy: 10-year experience. *J Endourol*, 2009. 23: 1409.
<https://www.ncbi.nlm.nih.gov/pubmed/19694529>
381. Nakada, S.Y., *et al.* Retrospective analysis of the effect of crossing vessels on successful retrograde endopyelotomy outcomes using spiral computerized tomography angiography. *J Urol*, 1998. 159: 62.
<https://www.ncbi.nlm.nih.gov/pubmed/9400437>
382. Skolarikos, A., *et al.* Ureteropelvic obstruction and renal stones: etiology and treatment. *Urolithiasis*, 2015. 43: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/25362543>
383. Reis-Santos, R.-S., Age of first stone episode., in *Urolithiasis*, Rodgers AL, Hess B, Khan SR, Preminger GM, Eds. 2000, University of Cape Town, Cape Town.
384. Robertson WG, *et al.*, Possible causes of the changing pattern of the age of onset of urinary stone disease in the UK., in *Urolithiasis*, Rodgers AL, Hess B, Khan SR, Preminger GM, Eds. 2000, University of Cape Town, Cape Town.
385. Djelloul, Z., *et al.* [Urinary stones in Western Algeria: study of the composition of 1,354 urinary stones in relation to their anatomical site and the age and gender of the patients]. *Prog Urol*, 2006. 16: 328.
<https://www.ncbi.nlm.nih.gov/pubmed/16821346>
386. Sarica, K. Pediatric urolithiasis: etiology, specific pathogenesis and medical treatment. *Urol Res*, 2006. 34: 96.
<https://www.ncbi.nlm.nih.gov/pubmed/16432692>
387. Sarica, K. Medical aspect and minimal invasive treatment of urinary stones in children. *Arch Ital Urol Androl*, 2008. 80: 43.
<https://www.ncbi.nlm.nih.gov/pubmed/18683808>
388. Sayasone, S., *et al.* Bladder stones in childhood: a descriptive study in a rural setting in Saravan Province, Lao PDR. *Southeast Asian J Trop Med Public Health*, 2004. 35 Suppl 2: 50.
<https://www.ncbi.nlm.nih.gov/pubmed/15906634>
389. Aldaqadossi, H.A., *et al.* Efficacy and safety of tamsulosin as a medical expulsive therapy for stones in children. *Arab J Urol*, 2015. 13: 107.
<https://www.ncbi.nlm.nih.gov/pubmed/26413330>
390. Aydogdu, O., *et al.* Effectiveness of doxazosin in treatment of distal ureteral stones in children. *J Urol*, 2009. 182: 2880.
<https://www.ncbi.nlm.nih.gov/pubmed/19846149>
391. Mokhless, I., *et al.* Tamsulosin for the management of distal ureteral stones in children: a prospective randomized study. *J Pediatr Urol*, 2012. 8: 544.
<https://www.ncbi.nlm.nih.gov/pubmed/22099477>
392. Glina, F.P., *et al.* The use of alpha-1 adrenergic blockers in children with distal ureterolithiasis: a systematic review and meta-analysis. *Int Braz J Urol*, 2015. 41: 1049.
<https://www.ncbi.nlm.nih.gov/pubmed/26717117>
393. Velazquez, N., *et al.* Medical expulsive therapy for pediatric urolithiasis: Systematic review and meta-analysis. *J Pediatr Urol*, 2015. 11: 321.
<https://www.ncbi.nlm.nih.gov/pubmed/26165192>
394. Lahme, S. Shockwave lithotripsy and endourological stone treatment in children. *Urol Res*, 2006. 34: 112.
<https://www.ncbi.nlm.nih.gov/pubmed/16446980>
395. Smaldone, M.C., *et al.* Contemporary surgical management of pediatric urolithiasis. *Urol Clin North Am*, 2010. 37: 253.
<https://www.ncbi.nlm.nih.gov/pubmed/20569803>
396. Landau, E.H., *et al.* Extracorporeal shock wave lithotripsy in prepubertal children: 22-year experience at a single institution with a single lithotripter. *J Urol*, 2009. 182: 1835.
<https://www.ncbi.nlm.nih.gov/pubmed/19692011>
397. Frick, J., *et al.* Long-term follow-up after extracorporeal shock wave lithotripsy in children. *Eur Urol*, 1991. 19: 225.
<https://www.ncbi.nlm.nih.gov/pubmed/1855529>

398. D'Addessi, A., *et al.* Is extracorporeal shock wave lithotripsy in pediatrics a safe procedure? *J Pediatr Surg*, 2008. 43: 591.
<https://www.ncbi.nlm.nih.gov/pubmed/18405701>
399. Lu, P., *et al.* The clinical efficacy of extracorporeal shock wave lithotripsy in pediatric urolithiasis: a systematic review and meta-analysis. *Urolithiasis*, 2015. 43: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/25721456>
400. Salem, H.K., *et al.* Slow vs rapid delivery rate shock wave lithotripsy for pediatric renal urolithiasis: a prospective randomized study. *J Urol*, 2014. 191: 1370.
<https://www.ncbi.nlm.nih.gov/pubmed/24262496>
401. Aldridge, R.D., *et al.* Anesthesia for pediatric lithotripsy. *Paediatr Anaesth*, 2006. 16: 236.
<https://www.ncbi.nlm.nih.gov/pubmed/16490086>
402. Sarica, K., *et al.* Long-term follow-up of renal morphology and function in children after lithotripsy. *Urol Int*, 1995. 54: 95.
<https://www.ncbi.nlm.nih.gov/pubmed/7747366>
403. Griffin, S.J., *et al.* Safety of shock wave lithotripsy for treatment of pediatric urolithiasis: 20-year experience. *J Urol*, 2010. 183: 2332.
<https://www.ncbi.nlm.nih.gov/pubmed/20400129>
404. Reisiger, K., *et al.* Pediatric nephrolithiasis: does treatment affect renal growth? *Urology*, 2007. 69: 1190.
<https://www.ncbi.nlm.nih.gov/pubmed/17572213>
405. Kurien, A., *et al.* Extracorporeal shock wave lithotripsy in children: equivalent clearance rates to adults is achieved with fewer and lower energy shock waves. *BJU Int*, 2009. 103: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/18727616>
406. Desai, M. Endoscopic management of stones in children. *Curr Opin Urol*, 2005. 15: 107.
<https://www.ncbi.nlm.nih.gov/pubmed/15725934>
407. Straub, M., *et al.* Pediatric urolithiasis: the current surgical management. *Pediatr Nephrol*, 2010. 25: 1239.
<https://www.ncbi.nlm.nih.gov/pubmed/20130924>
408. Smaldone, M.C., *et al.* Endourological management of pediatric stone disease: present status. *J Urol*, 2009. 181: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/19012920>
409. Kapoor, R., *et al.* Safety and efficacy of percutaneous nephrolithotomy in the pediatric population. *J Endourol*, 2008. 22: 637.
<https://www.ncbi.nlm.nih.gov/pubmed/18338958>
410. Hosseini, S.R., *et al.* One shot tract dilation for percutaneous nephrolithotomy: is it safe and effective in preschool children? *Urol Int*, 2014. 92: 440.
<https://www.ncbi.nlm.nih.gov/pubmed/24603110>
411. Song, G., *et al.* Advantages of tubeless mini-percutaneous nephrolithotomy in the treatment of preschool children under 3 years old. *J Pediatr Surg*, 2015. 50: 655.
<https://www.ncbi.nlm.nih.gov/pubmed/25840082>
412. Samad, L., *et al.* Tubed vs tubeless PCNL in children. *J Pak Med Assoc*, 2012. 62: 892.
<https://www.ncbi.nlm.nih.gov/pubmed/23139970>
413. Cannon, G.M., *et al.* Ureteroscopic management of lower-pole stones in a pediatric population. *J Endourol*, 2007. 21: 1179.
<https://www.ncbi.nlm.nih.gov/pubmed/17949321>
414. Erturhan, S., *et al.* Ureteroscopic management of ureteral calculi in children. *J Endourol*, 2007. 21: 397.
<https://www.ncbi.nlm.nih.gov/pubmed/17451329>
415. Basiri, A., *et al.* A multicenter, randomized, controlled trial of transureteral and shock wave lithotripsy--which is the best minimally invasive modality to treat distal ureteral calculi in children? *J Urol*, 2010. 184: 1106.
<https://www.ncbi.nlm.nih.gov/pubmed/20650490>
416. Basiri, A., *et al.* Ureteral calculi in children: what is best as a minimally invasive modality? *Urol J*, 2008. 5: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/18592456>
417. Ishii, H., *et al.* Ureteroscopy for stone disease in the paediatric population: a systematic review. *BJU Int*, 2015. 115: 867.
<https://www.ncbi.nlm.nih.gov/pubmed/25203925>

418. Safwat, A.S., *et al.* Experience with ureteroscopic holmium laser lithotripsy in children. *Pediatr Surg Int*, 2008. 24: 579.
<https://www.ncbi.nlm.nih.gov/pubmed/18365216>
419. Kim, S.S., *et al.* Pediatric flexible ureteroscopic lithotripsy: the children's hospital of Philadelphia experience. *J Urol*, 2008. 180: 2616.
<https://www.ncbi.nlm.nih.gov/pubmed/18950810>
420. Ishii, H., *et al.* Flexible ureteroscopy and lasertripsy (FURSL) for paediatric renal calculi: results from a systematic review. *J Pediatr Urol*, 2014. 10: 1020.
<https://www.ncbi.nlm.nih.gov/pubmed/25241397>
421. Mokhless, I.A., *et al.* Retrograde intrarenal surgery monotherapy versus shock wave lithotripsy for stones 10 to 20 mm in preschool children: a prospective, randomized study. *J Urol*, 2014. 191: 1496.
<https://www.ncbi.nlm.nih.gov/pubmed/24679882>
422. Gokce, M.I., *et al.* Effect of Prestering on Success and Complication Rates of Ureterorenoscopy in Pediatric Population. *J Endourol*, 2016. 30: 850.
<https://www.ncbi.nlm.nih.gov/pubmed/27189236>
423. Saad, K.S., *et al.* Percutaneous Nephrolithotomy vs Retrograde Intrarenal Surgery for Large Renal Stones in Pediatric Patients: A Randomized Controlled Trial. *J Urol*, 2015. 194: 1716.
<https://www.ncbi.nlm.nih.gov/pubmed/26165587>
424. Muslumanoglu, A.Y., *et al.* Extracorporeal shock wave lithotripsy as first line treatment alternative for urinary tract stones in children: a large scale retrospective analysis. *J Urol*, 2003. 170: 2405.
<https://www.ncbi.nlm.nih.gov/pubmed/14634438>
425. Casale, P., *et al.* Transperitoneal laparoscopic pyelolithotomy after failed percutaneous access in the pediatric patient. *J Urol*, 2004. 172: 680.
<https://www.ncbi.nlm.nih.gov/pubmed/15247760>
426. Fragoso, A.C., *et al.* Minimal access surgery in the management of pediatric urolithiasis. *J Pediatr Urol*, 2009. 5: 42.
<https://www.ncbi.nlm.nih.gov/pubmed/18805739>
427. Elderwy, A.A., *et al.* Dissolution therapy versus shock wave lithotripsy for radiolucent renal stones in children: a prospective study. *J Urol*, 2014. 191: 1491.
<https://www.ncbi.nlm.nih.gov/pubmed/24679880>
428. Sarica, K., *et al.* Effect of potassium citrate therapy on stone recurrence and regrowth after extracorporeal shockwave lithotripsy in children. *J Endourol*, 2006. 20: 875.
<https://www.ncbi.nlm.nih.gov/pubmed/17144854>
429. Parks, J.H., *et al.* A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. *J Urol*, 2002. 167: 1607.
<https://www.ncbi.nlm.nih.gov/pubmed/11912373>
430. Nayan, M., *et al.* Variations between two 24-hour urine collections in patients presenting to a tertiary stone clinic. *Can Urol Assoc J*, 2012. 6: 30.
<https://www.ncbi.nlm.nih.gov/pubmed/22396364>
431. Ferraz, R.R., *et al.* Preservation of urine samples for metabolic evaluation of stone-forming patients. *Urol Res*, 2006. 34: 329.
<https://www.ncbi.nlm.nih.gov/pubmed/16896690>
432. Yilmaz, G., *et al.* Are preservatives necessary in 24-hour urine measurements? *Clin Biochem*, 2008. 41: 899.
<https://www.ncbi.nlm.nih.gov/pubmed/18371307>
433. Coe, F.L., *et al.* Kidney stone disease. *J Clin Invest*, 2005. 115: 2598.
<https://www.ncbi.nlm.nih.gov/pubmed/16200192>
434. Norman, R.W., *et al.* When should patients with symptomatic urinary stone disease be evaluated metabolically? *J Urol*, 1984. 132: 1137.
<https://www.ncbi.nlm.nih.gov/pubmed/6502804>
435. Assimios, D., *et al.* Urine evaluation. In: 2nd International Consultation on Stone Disease. Denstedt J, Khoury S, Eds. Health Publications 2007.
436. Hesse A, *et al.* Urinary Stones: Diagnosis, Treatment and Prevention of Recurrence., in Uric acid stones. 2002, S Karger AG,; Basel.
437. Tiselius, H.G. Standardized estimate of the ion activity product of calcium oxalate in urine from renal stone formers. *Eur Urol*, 1989. 16: 48.
<https://www.ncbi.nlm.nih.gov/pubmed/2714318>

438. Ackermann, D., *et al.* Use of the computer program EQUIL to estimate pH in model solutions and human urine. *Urol Res*, 1989. 17: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/2749945>
439. Kavanagh, J.P., *et al.* Why does the Bonn Risk Index discriminate between calcium oxalate stone formers and healthy controls? *J Urol*, 2006. 175: 766.
<https://www.ncbi.nlm.nih.gov/pubmed/16407047>
440. Rodgers AL, *et al.* What can it teach us?, in Proceedings of Renal Stone Disease 1st Annual International Urolithiasis Research Symposium, 2-3 November 2006., J.L.a.J.W. AP Evan, Jr, Editor. 2007, American Institute of Physics: Melville, New York
441. Hoppe, B., *et al.* Diagnostic examination of the child with urolithiasis or nephrocalcinosis. *Pediatr Nephrol*, 2010. 25: 403.
<https://www.ncbi.nlm.nih.gov/pubmed/19104842>
442. Borghi, L., *et al.* Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J Urol*, 1996. 155: 839.
<https://www.ncbi.nlm.nih.gov/pubmed/8583588>
443. Sarica, K., *et al.* The effect of calcium channel blockers on stone regrowth and recurrence after shock wave lithotripsy. *Urol Res*, 2006. 34: 184.
<https://www.ncbi.nlm.nih.gov/pubmed/16463053>
444. Fink, H.A., *et al.* Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. *Ann Intern Med*, 2013. 158: 535.
<https://www.ncbi.nlm.nih.gov/pubmed/23546565>
445. Siener, R., *et al.* Dietary risk factors for hyperoxaluria in calcium oxalate stone formers. *Kidney Int*, 2003. 63: 1037.
<https://www.ncbi.nlm.nih.gov/pubmed/12631085>
446. Wabner, C.L., *et al.* Effect of orange juice consumption on urinary stone risk factors. *J Urol*, 1993. 149: 1405.
<https://www.ncbi.nlm.nih.gov/pubmed/8501777>
447. Gettman, M.T., *et al.* Effect of cranberry juice consumption on urinary stone risk factors. *J Urol*, 2005. 174: 590.
<https://www.ncbi.nlm.nih.gov/pubmed/16006907>
448. Shuster, J., *et al.* Soft drink consumption and urinary stone recurrence: a randomized prevention trial. *J Clin Epidemiol*, 1992. 45: 911.
<https://www.ncbi.nlm.nih.gov/pubmed/1624973>
449. Kocvara, R., *et al.* A prospective study of nonmedical prophylaxis after a first kidney stone. *BJU Int*, 1999. 84: 393.
<https://www.ncbi.nlm.nih.gov/pubmed/10468751>
450. Hess, B., *et al.* Effects of a 'common sense diet' on urinary composition and supersaturation in patients with idiopathic calcium urolithiasis. *Eur Urol*, 1999. 36: 136.
<https://www.ncbi.nlm.nih.gov/pubmed/10420035>
451. Ebisuno, S., *et al.* Results of long-term rice bran treatment on stone recurrence in hypercalciuric patients. *Br J Urol*, 1991. 67: 237.
<https://www.ncbi.nlm.nih.gov/pubmed/1902388>
452. Hiatt, R.A., *et al.* Randomized controlled trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. *Am J Epidemiol*, 1996. 144: 25.
<https://www.ncbi.nlm.nih.gov/pubmed/8659482>
453. Dussol, B., *et al.* A randomized trial of low-animal-protein or high-fiber diets for secondary prevention of calcium nephrolithiasis. *Nephron Clin Pract*, 2008. 110: c185.
<https://www.ncbi.nlm.nih.gov/pubmed/18957869>
454. Turney, B.W., *et al.* Diet and risk of kidney stones in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC). *Eur J Epidemiol*, 2014. 29: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/24752465>
455. Auer, B.L., *et al.* The effect of ascorbic acid ingestion on the biochemical and physicochemical risk factors associated with calcium oxalate kidney stone formation. *Clin Chem Lab Med*, 1998. 36: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/9589801>
456. Borghi, L., *et al.* Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med*, 2002. 346: 77.
<https://www.ncbi.nlm.nih.gov/pubmed/11784873>
457. Fink, H.A., *et al.* Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. *Eur Urol*, 2009. 56: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/19321253>

458. Curhan, G.C., *et al.* Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med*, 1997. 126: 497.
<https://www.ncbi.nlm.nih.gov/pubmed/9092314>
459. von Unruh, G.E., *et al.* Dependence of oxalate absorption on the daily calcium intake. *J Am Soc Nephrol*, 2004. 15: 1567.
<https://www.ncbi.nlm.nih.gov/pubmed/15153567>
460. Harris, S.S., *et al.* Effects of Hydration and Calcium Supplementation on Urine Calcium Concentration in Healthy Postmenopausal Women. *J Am Coll Nutr*, 2015. 34: 340.
<https://www.ncbi.nlm.nih.gov/pubmed/25856469>
461. Curhan, G.C., *et al.* A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med*, 1993. 328: 833.
<https://www.ncbi.nlm.nih.gov/pubmed/8441427>
462. Coe, F.L. Hyperuricosuric calcium oxalate nephrolithiasis. *Adv Exp Med Biol*, 1980. 128: 439.
<https://www.ncbi.nlm.nih.gov/pubmed/7424690>
463. Hyperuricosuric calcium stone disease, in *Kidney Stones: Medical and Surgical Management*, F.M. Coe FL, Pak CYC, Parks JH, Preminger GM, Editor. 1996, Lippincott-Raven: Philadelphia.
464. Siener, R., *et al.* The role of overweight and obesity in calcium oxalate stone formation. *Obes Res*, 2004. 12: 106.
<https://www.ncbi.nlm.nih.gov/pubmed/14742848>
465. Madore, F., *et al.* Nephrolithiasis and risk of hypertension. *Am J Hypertens*, 1998. 11: 46.
<https://www.ncbi.nlm.nih.gov/pubmed/9504449>
466. Madore, F., *et al.* Nephrolithiasis and risk of hypertension in women. *Am J Kidney Dis*, 1998. 32: 802.
<https://www.ncbi.nlm.nih.gov/pubmed/9820450>
467. Tiselius, H.G., *et al.* Effects of citrate on the different phases of calcium oxalate crystallization. *Scanning Microsc*, 1993. 7: 381.
<https://www.ncbi.nlm.nih.gov/pubmed/8316807>
468. Barcelo, P., *et al.* Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol*, 1993. 150: 1761.
<https://www.ncbi.nlm.nih.gov/pubmed/8230497>
469. Hofbauer, J., *et al.* Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis--a prospective randomized study. *Br J Urol*, 1994. 73: 362.
<https://www.ncbi.nlm.nih.gov/pubmed/8199822>
470. Ettinger, B., *et al.* Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol*, 1997. 158: 2069.
<https://www.ncbi.nlm.nih.gov/pubmed/9366314>
471. Soygur, T., *et al.* Effect of potassium citrate therapy on stone recurrence and residual fragments after shockwave lithotripsy in lower caliceal calcium oxalate urolithiasis: a randomized controlled trial. *J Endourol*, 2002. 16: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/12028622>
472. Premgamone, A., *et al.* A long-term study on the efficacy of a herbal plant, *Orthosiphon grandiflorus*, and sodium potassium citrate in renal calculi treatment. *Southeast Asian J Trop Med Public Health*, 2001. 32: 654.
<https://www.ncbi.nlm.nih.gov/pubmed/11944733>
473. Lojanapiwat, B., *et al.* Alkaline citrate reduces stone recurrence and regrowth after shockwave lithotripsy and percutaneous nephrolithotomy. *Int Braz J Urol*, 2011. 37: 611.
<https://www.ncbi.nlm.nih.gov/pubmed/22099273>
474. Phillips, R., *et al.* Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev*, 2015: CD010057.
<https://www.ncbi.nlm.nih.gov/pubmed/26439475>
475. Favus, M.J., *et al.* The effects of allopurinol treatment on stone formation on hyperuricosuric calcium oxalate stone-formers. *Scand J Urol Nephrol Suppl*, 1980. 53: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/6938003>
476. Miano L, *et al.* A placebo controlled double-blind study of allopurinol in severe recurrent idiopathic renal lithiasis, in *Urolithiasis and Related Clinical Research*, S.L. Schwille PO, Robertson WG, Vahlensieck W., Editor. 1985, Plenum Press: New York.
477. Ettinger, B., *et al.* Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med*, 1986. 315: 1386.
<https://www.ncbi.nlm.nih.gov/pubmed/3534570>

478. Robertson, W.G., *et al.* A Multicentre Trial to Evaluate Three Treatments for Recurrent Idiopathic Calcium Stone Disease — A Preliminary Report, in *Urolithiasis and Related Clinical Research*, P. Schuille, L. Smith, W. Robertson & W. Vahlensieck, Editors. 1985, Springer US.
479. Smith, M.J. Placebo versus allopurinol for renal calculi. *J Urol*, 1977. 117: 690.
<https://www.ncbi.nlm.nih.gov/pubmed/875139>
480. Cohen, T.D., *et al.* Clinical effect of captopril on the formation and growth of cystine calculi. *J Urol*, 1995. 154: 164.
<https://www.ncbi.nlm.nih.gov/pubmed/7776415>
481. Coulthard, M.G., *et al.* The treatment of cystinuria with captopril. *Am J Kidney Dis*, 1995. 25: 661.
<https://www.ncbi.nlm.nih.gov/pubmed/7702068>
482. Goldfarb, D.S., *et al.* Randomized controlled trial of febuxostat versus allopurinol or placebo in individuals with higher urinary uric acid excretion and calcium stones. *Clin J Am Soc Nephrol*, 2013. 8: 1960.
<https://www.ncbi.nlm.nih.gov/pubmed/23929928>
483. Nouvenne, A., *et al.* New pharmacologic approach to patients with idiopathic calcium nephrolithiasis and high uricosuria: Febuxostat vs allopurinol. A pilot study. *Eur J Int Med*. 24: e64.
[http://www.ejinme.com/article/S0953-6205\(13\)00364-6/abstract](http://www.ejinme.com/article/S0953-6205(13)00364-6/abstract)
484. Jarrar, K., *et al.* Struvite stones: long term follow up under metaphylaxis. *Ann Urol (Paris)*, 1996. 30: 112.
<https://www.ncbi.nlm.nih.gov/pubmed/8766146>
485. Hesse, A., *et al.* Causes of phosphate stone formation and the importance of metaphylaxis by urinary acidification: a review. *World J Urol*, 1999. 17: 308.
<https://www.ncbi.nlm.nih.gov/pubmed/10552150>
486. Ettinger, B., *et al.* Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. *J Urol*, 1988. 139: 679.
<https://www.ncbi.nlm.nih.gov/pubmed/3280829>
487. Prien, E.L., Sr., *et al.* Magnesium oxide-pyridoxine therapy for recurrent calcium oxalate calculi. *J Urol*, 1974. 112: 509.
<https://www.ncbi.nlm.nih.gov/pubmed/4414543>
488. Pinheiro, V.B., *et al.* The effect of sodium bicarbonate upon urinary citrate excretion in calcium stone formers. *Urology*, 2013. 82: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/23602798>
489. Hoppe, B., *et al.* The primary hyperoxalurias. *Kidney Int*, 2009. 75: 1264.
<https://www.ncbi.nlm.nih.gov/pubmed/19225556>
490. Borghi, L., *et al.* Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. *J Cardiovasc Pharmacol*, 1993. 22 Suppl 6: S78.
<https://www.ncbi.nlm.nih.gov/pubmed/7508066>
491. Brocks, P., *et al.* Do thiazides prevent recurrent idiopathic renal calcium stones? *Lancet*, 1981. 2: 124.
<https://www.ncbi.nlm.nih.gov/pubmed/6361755>
492. Mortensen, J.T., *et al.* Thiazides in the prophylactic treatment of recurrent idiopathic kidney stones. *Int Urol Nephrol*, 1986. 18: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/3533825>
493. Laerum, E., *et al.* Thiazide prophylaxis of urolithiasis. A double-blind study in general practice. *Acta Med Scand*, 1984. 215: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/6375276>
494. Ohkawa, M., *et al.* Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. *Br J Urol*, 1992. 69: 571.
<https://www.ncbi.nlm.nih.gov/pubmed/1638340>
495. Scholz, D., *et al.* Double-blind study with thiazide in recurrent calcium lithiasis. *J Urol*, 1982. 128: 903.
<https://www.ncbi.nlm.nih.gov/pubmed/7176047>
496. Nicar, M.J., *et al.* Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. *J Urol*, 1984. 131: 430.
<https://www.ncbi.nlm.nih.gov/pubmed/6699979>
497. Fernandez-Rodriguez, A., *et al.* [The role of thiazides in the prophylaxis of recurrent calcium lithiasis]. *Actas Urol Esp*, 2006. 30: 305.
<https://www.ncbi.nlm.nih.gov/pubmed/16749588>

498. Ahlstrand, C., *et al.* Prophylactic treatment of calcium-stone-formers with hydrochlorothiazide and magnesium., in *Renal Stones—Aspects on Their Formation, Removal and Prevention*, H.G. Tiselius, Editor. 1996, Akademityrck AB: Edsbruk, Sweden.
499. Dolin, D.J., *et al.* Effect of cystine-binding thiol drugs on urinary cystine capacity in patients with cystinuria. *J Endourol*, 2005. 19: 429.
<https://www.ncbi.nlm.nih.gov/pubmed/15865542>
500. Chow, G.K., *et al.* Medical treatment of cystinuria: results of contemporary clinical practice. *J Urol*, 1996. 156: 1576.
<https://www.ncbi.nlm.nih.gov/pubmed/8863541>
501. Pak, C.Y., *et al.* Management of cystine nephrolithiasis with alpha-mercaptopyronylglycine. *J Urol*, 1986. 136: 1003.
<https://www.ncbi.nlm.nih.gov/pubmed/3534301>
502. Tekin, A., *et al.* Cystine calculi in children: the results of a metabolic evaluation and response to medical therapy. *J Urol*, 2001. 165: 2328.
<https://www.ncbi.nlm.nih.gov/pubmed/11371943>
503. Worcester, E.M., *et al.* New insights into the pathogenesis of idiopathic hypercalciuria. *Semin Nephrol*, 2008. 28: 120.
<https://www.ncbi.nlm.nih.gov/pubmed/18359393>
504. Wolf, H., *et al.* Do thiazides prevent recurrent idiopathic renal calcium oxalate stones? *Proc Eur Dial Transplant Assoc*, 1983. 20: 477.
<https://www.ncbi.nlm.nih.gov/pubmed/6361755>
505. Johansson, G., *et al.* Effects of magnesium hydroxide in renal stone disease. *J Am Coll Nutr*, 1982. 1: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/6764473>
506. Khan, S.R., *et al.* Magnesium oxide administration and prevention of calcium oxalate nephrolithiasis. *J Urol*, 1993. 149: 412.
<https://www.ncbi.nlm.nih.gov/pubmed/8426432>
507. Pearle, M.S., *et al.* Meta-analysis of randomized trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol*, 1999. 13: 679.
<https://www.ncbi.nlm.nih.gov/pubmed/10608521>
508. Silverberg, S.J., *et al.* A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med*, 1999. 341: 1249.
<https://www.ncbi.nlm.nih.gov/pubmed/10528034>
509. Mollerup, C.L., *et al.* Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *Bmj*, 2002. 325: 807.
<https://www.ncbi.nlm.nih.gov/pubmed/12376441>
510. Evan, A.E., *et al.* Histopathology and surgical anatomy of patients with primary hyperparathyroidism and calcium phosphate stones. *Kidney Int*, 2008. 74: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/18449170>
511. Rizzato, G., *et al.* Nephrolithiasis as a presenting feature of chronic sarcoidosis: a prospective study. *Sarcoidosis Vasc Diffuse Lung Dis*, 1996. 13: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/8893387>
512. Takei, K., *et al.* Oral calcium supplement decreases urinary oxalate excretion in patients with enteric hyperoxaluria. *Urol Int*, 1998. 61: 192.
<https://www.ncbi.nlm.nih.gov/pubmed/9933846>
513. Domrongkitchaiporn, S., *et al.* Dosage of potassium citrate in the correction of urinary abnormalities in pediatric distal renal tubular acidosis patients. *Am J Kidney Dis*, 2002. 39: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/11840381>
514. Peter Maxwell A. Genetic renal abnormalities. *Medicine*, 2007. 35: 386.
[http://www.medicinejournal.co.uk/article/S1357-3039\(07\)00109-0/abstract](http://www.medicinejournal.co.uk/article/S1357-3039(07)00109-0/abstract)
515. Mandel, N.S., *et al.* Urinary tract stone disease in the United States veteran population. II. Geographical analysis of variations in composition. *J Urol*, 1989. 142: 1516.
<https://www.ncbi.nlm.nih.gov/pubmed/2585627>
516. Cameron, M.A., *et al.* Uric acid nephrolithiasis. *Urol Clin North Am*, 2007. 34: 335.
<https://www.ncbi.nlm.nih.gov/pubmed/17678984>
517. Millman, S., *et al.* Pathogenesis and clinical course of mixed calcium oxalate and uric acid nephrolithiasis. *Kidney Int*, 1982. 22: 366.
<https://www.ncbi.nlm.nih.gov/pubmed/7176335>

518. Pak, C.Y., *et al.* Biochemical distinction between hyperuricosuric calcium urolithiasis and gouty diathesis. *Urology*, 2002. 60: 789.
<https://www.ncbi.nlm.nih.gov/pubmed/12429297>
519. Chou, Y.H., *et al.* Clinical study of ammonium acid urate urolithiasis. *Kaohsiung J Med Sci*, 2012. 28: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/22531304>
520. Wagner, C.A., *et al.* Urinary pH and stone formation. *J Nephrol*, 2010. 23 Suppl 16: S165.
<https://www.ncbi.nlm.nih.gov/pubmed/21170875>
521. Miano, R., *et al.* Stones and urinary tract infections. *Urol Int*, 2007. 79 Suppl 1: 32.
<https://www.ncbi.nlm.nih.gov/pubmed/17726350>
522. Rodman JS, *et al.* Diagnosis and treatment of uric acid calculi., in *Kidney Stones. Medical and Surgical Management*, F.M. Coe FL, Pak CYC, Parks JH, Preminger GM., Editor. 1996, Lippincott-Raven: Philadelphia.
523. Low, R.K., *et al.* Uric acid-related nephrolithiasis. *Urol Clin North Am*, 1997. 24: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/9048857>
524. Shekarriz, B., *et al.* Uric acid nephrolithiasis: current concepts and controversies. *J Urol*, 2002. 168: 1307.
<https://www.ncbi.nlm.nih.gov/pubmed/12352383>
525. Pak, C.Y., *et al.* Mechanism for calcium urolithiasis among patients with hyperuricosuria: supersaturation of urine with respect to monosodium urate. *J Clin Invest*, 1977. 59: 426.
<https://www.ncbi.nlm.nih.gov/pubmed/14173>
526. Wilcox, W.R., *et al.* Solubility of uric acid and monosodium urate. *Med Biol Eng*, 1972. 10: 522.
<https://www.ncbi.nlm.nih.gov/pubmed/5074854>
527. Mattle, D., *et al.* Preventive treatment of nephrolithiasis with alkali citrate--a critical review. *Urol Res*, 2005. 33: 73.
<https://www.ncbi.nlm.nih.gov/pubmed/15875173>
528. Marchini, G.S., *et al.* Gout, stone composition and urinary stone risk: a matched case comparative study. *J Urol*, 2013. 189: 1334.
<https://www.ncbi.nlm.nih.gov/pubmed/23022002>
529. Kramer, G., *et al.* Role of bacteria in the development of kidney stones. *Curr Opin Urol*, 2000. 10: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/10650513>
530. Gettman, M.T., *et al.* Struvite stones: diagnosis and current treatment concepts. *J Endourol*, 1999. 13: 653.
<https://www.ncbi.nlm.nih.gov/pubmed/10608517>
531. Bichler, K.H., *et al.* Urinary infection stones. *Int J Antimicrob Agents*, 2002. 19: 488.
<https://www.ncbi.nlm.nih.gov/pubmed/12135839>
532. Carpentier, X., *et al.* Relationships between carbonation rate of carbapatite and morphologic characteristics of calcium phosphate stones and etiology. *Urology*, 2009. 73: 968.
<https://www.ncbi.nlm.nih.gov/pubmed/19394492>
533. Thompson, R.B., *et al.* Bacteriology of infected stones. *Urology*, 1973. 2: 627.
<https://www.ncbi.nlm.nih.gov/pubmed/4587909>
534. McLean, R.J., *et al.* The ecology and pathogenicity of urease-producing bacteria in the urinary tract. *Crit Rev Microbiol*, 1988. 16: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/3053050>
535. Wong HY, *et al.* Medical management and prevention of struvite stones, in *Kidney Stones: Medical and Surgical Management*, Coe & F.M. FL, Pak CYC, Parks JH, Preminger GM., Editors. 1996, Lippincott-Raven: Philadelphia.
536. Wall, I., *et al.* Long-term acidification of urine in patients treated for infected renal stones. *Urol Int*, 1990. 45: 336.
<https://www.ncbi.nlm.nih.gov/pubmed/2288050>
537. Griffith, D.P., *et al.* Randomized, double-blind trial of Lithostat (acetohydroxamic acid) in the palliative treatment of infection-induced urinary calculi. *Eur Urol*, 1991. 20: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/1726639>
538. Williams, J.J., *et al.* A randomized double-blind study of acetohydroxamic acid in struvite nephrolithiasis. *N Engl J Med*, 1984. 311: 760.
<https://www.ncbi.nlm.nih.gov/pubmed/6472365>
539. Milliner, D.S., *et al.* Urolithiasis in pediatric patients. *Mayo Clin Proc*, 1993. 68: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/8474265>
540. Rogers, A., *et al.* Management of cystinuria. *Urol Clin North Am*, 2007. 34: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/17678985>

541. Dello Strologo, L., *et al.* Comparison between SLC3A1 and SLC7A9 cystinuria patients and carriers: a need for a new classification. *J Am Soc Nephrol*, 2002. 13: 2547.
<https://www.ncbi.nlm.nih.gov/pubmed/12239244>
542. Lee, W.S., *et al.* Cloning and chromosomal localization of a human kidney cDNA involved in cystine, dibasic, and neutral amino acid transport. *J Clin Invest*, 1993. 91: 1959.
<https://www.ncbi.nlm.nih.gov/pubmed/8486766>
543. Knoll, T., *et al.* Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. *Pediatr Nephrol*, 2005. 20: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/15602663>
544. Nakagawa, Y., *et al.* Clinical use of cystine supersaturation measurements. *J Urol*, 2000. 164: 1481.
<https://www.ncbi.nlm.nih.gov/pubmed/11025687>
545. Fjellstedt, E., *et al.* Cystine analyses of separate day and night urine as a basis for the management of patients with homozygous cystinuria. *Urol Res*, 2001. 29: 303.
<https://www.ncbi.nlm.nih.gov/pubmed/11762791>
546. Ng, C.S., *et al.* Contemporary management of cystinuria. *J Endourol*, 1999. 13: 647.
<https://www.ncbi.nlm.nih.gov/pubmed/10608516>
547. Biyani, C.S., *et al.* Cystinuria—diagnosis and management. *EAU-EBU Update Series* 2006. 4: 175.
<https://www.ncbi.nlm.nih.gov/pubmed/>
548. Matlaga, B.R., *et al.* Drug-induced urinary calculi. *Rev Urol*, 2003. 5: 227.
http://eu-acme.org/europanurology/upload_articles/Cystinuria.pdf
549. Finocchiaro, R., *et al.* Usefulness of cyanide-nitroprusside test in detecting incomplete recessive heterozygotes for cystinuria: a standardized dilution procedure. *Urol Res*, 1998. 26: 401.
<https://www.ncbi.nlm.nih.gov/pubmed/9879820>
550. Nakagawa, Y., *et al.* A modified cyanide-nitroprusside method for quantifying urinary cystine concentration that corrects for creatinine interference. *Clin Chim Acta*, 1999. 289: 57.
<https://www.ncbi.nlm.nih.gov/pubmed/10556653>

6. CONFLICT OF INTEREST

All members of the Urolithiasis Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/online-guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Paediatric Urology

S. Tekgül (Chair), H.S. Dogan, R. Kocvara,
J.M. Nijman (Vice-chair), C. Radmayr, R. Stein
Guidelines Associates: M.S. Silay,
S. Undre, J. Quaedackers



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1. INTRODUCTION

1.1 Aim

A collaborative working group consisting of members representing the European Society for Paediatric Urology (ESPU) and the European Association of Urology (EAU) has prepared these Guidelines with the aim of increasing the quality of care for children with urological conditions. This Guideline document addresses a number of common clinical pathologies in paediatric urological practice, as covering the entire field of paediatric urology in a single guideline document is unattainable.

The majority of urological clinical problems in children are distinct and in many ways differ to those in adults. This publication intends to outline a practical and preliminary approach to paediatric urological conditions. Complex and rare conditions that require special care with experienced doctors should be referred to designated centres where paediatric urology practice has been fully established and a multidisciplinary approach is available.

Over time, paediatric urology has informally developed and matured, establishing its diverse body of knowledge and expertise and may now be ready to distinguish itself from its parent specialties. Thus, paediatric urology has recently emerged in many European countries as a distinct subspecialty of both urology and paediatric surgery and presents a unique challenge in the sense that it covers a large area with many different schools of thought and a huge diversity in management.

Knowledge gained by increasing experience, new technological advances and non-invasive diagnostic screening modalities has had a profound influence on treatment modalities in paediatric urology, a trend that is likely to continue in the years to come.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of children and their care-givers into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU-ESPU Paediatric Urology Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website Uroweb: <http://uroweb.org/guideline/paediatric-urology/>.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal are also available [1-3]. All documents can be viewed through the EAU website: <http://uroweb.org/guideline/paediatric-urology/>.

1.4 Publication history

The Paediatric Urology Guidelines were first published in 2001. This 2017 publication includes a number of updated chapters and sections as detailed below.

1.5 Summary of changes

The literature for the complete document has been assessed and updated, wherever relevant.

Key changes in the 2017 publication:

- Section 3.4 - Acute scrotum in children: The literature has been updated resulting in minor revisions to the text;
- Section 3.5 - Hypospadias: Both the literature and the text have been revised extensively;
- Section 3.6 - Congenital penile curvature: Both the literature and the text have been revised extensively;
- 3.12 - Dilatation of the upper urinary tract (UUT) (UPJ and UVJ obstruction). A new section presenting the results of a systematic review interrogating the role of antibiotic prophylaxis in antenatal hydronephrosis has been included [4];
- Section 3.14 - Urinary stone disease: Both the literature and the text have been revised extensively.

1.5.1 **New and changed recommendations**3.6.4 **Summary of evidence and recommendations for the management of congenital penile curvature**

Summary of evidence	LE
Isolated congenital penile curvature is relatively uncommon.	2a
Congenital penile curvature is often associated with hypospadias.	2a
Diagnosis is usually made late in childhood.	2a
The penis only appears abnormal when erect.	1b
Congenital penile curvature can cause aesthetic as well as functional sexual problems.	1b
Congenital penile curvature is treated with surgery.	1b
The goal of surgery is to achieve corpora of similar size.	1b

Recommendations	LE	GR
Ensure that a thorough medical history is taken and a full clinical examination done to rule out associated anomalies in boys presenting with congenital curvature.	1a	A
Provide photo documentation of the erect penis from different angles as a prerequisite in the pre-operative evaluation.	1b	A
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	2b	B
At the beginning as well as at the end of surgery perform artificial erection tests.	2a	A

3.5.6 **Summary of evidence and recommendations for the management of hypospadias**

Summary of evidence	LE
Androgen stimulation therapy results in increased penile length and glans circumference.	1B
The complication rate is about 10% in distal and 25% in proximal hypospadias one-stage repairs. Higher and variable rate (between 28 and 68%) can occur in two-stage repairs.	3

Recommendations	GR
In children diagnosed with proximal hypospadias and a small appearing penis, reduced glans circumference or reduced urethral plate, pre-operative hormonal androgen stimulation treatment is an option and the body of evidence to accentuate its harms and benefits is inadequate.	B
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature.	A
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	A

3.12.5 **Summary of evidence and recommendations for the management of ureteropelvic junction (UPJ)-, UVJ-obstruction**

Summary of evidence	LE
In children diagnosed with antenatal hydronephrosis, a systematic review could not establish any benefits or harms related to continuous antibiotic prophylaxis.	1b
In children diagnosed with antenatal hydronephrosis, non-circumcised infants (LE: 1a), children diagnosed with high-grade hydronephrosis (LE: 2) and hydroureteronephrosis (LE: 1b) were shown to be at higher risk of developing UTI.	2

Recommendation	LE	GR
Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection (uncircumcised infants (LE: 1a), children diagnosed with hydroureteronephrosis (LE: 1b) and high-grade hydronephrosis (LE: 2).	2	A

2. METHODS

These Guidelines were compiled based on current literature following a structured review using MEDLINE. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. The limited availability of large randomised controlled trials (RCTs) - influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different congenital problems - means this document is largely a consensus document. Clearly there is a need for continuous re-evaluation of the information presented in this document.

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>. A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.1 Peer review

The following section was peer-reviewed prior to publication:

- Chapter 3.2 - Undescended testes.

All other chapters of the Paediatric Urology Guidelines were peer-reviewed in 2015.

2.2 Future goals

The Paediatric Urology Guidelines Panel aim to systematically address the following key clinical topic in a future update of the Guidelines:

- What are the short-term and long-term benefits and harms of varicocele intervention in children?

3. THE GUIDELINE

3.1 Phimosis

3.1.1 *Epidemiology, aetiology and pathophysiology*

At the end of the first year of life, retraction of the foreskin behind the glandular sulcus is possible in approximately 50% of boys; this rises to approximately 89% by the age of three years. The incidence of phimosis is 8% in six to seven year olds and just 1% in males aged sixteen to eighteen years [6].

3.1.2 *Classification systems*

The phimosis is either primary with no sign of scarring, or secondary (pathological) to a scarring such as balanitis xerotica obliterans (BXO) [6]. Balanitis xerotica obliterans, also termed lichen sclerosis, has been recently found in 17% of boys younger than ten years presenting with phimosis. The clinical appearance of BXO in children may be confusing and does not correlate with the final histopathological results. Chronic inflammation was the most common finding [7] (LE: 2b).

Phimosis has to be distinguished from normal agglutination of the foreskin to the glans, which is a more or less lasting physiological phenomenon with clearly-visible meatus and free partial retraction [8]. Paraphimosis must be regarded as an emergency situation: retraction of a too narrow prepuce behind the glans penis into the glanular sulcus may constrict the shaft and lead to oedema of the glans and retracted foreskin. It interferes with perfusion distally from the constrictive ring and brings a risk of preputial necrosis.

3.1.3 *Diagnostic evaluation*

The diagnosis of phimosis and paraphimosis is made by physical examination. If the prepuce is not retractable, or only partly retractable, and shows a constrictive ring on drawing back over the glans penis, a disproportion between the width of the foreskin and the diameter of the glans penis has to be assumed. In addition to the constricted foreskin, there may be adhesions between the inner surface of the prepuce and the glanular epithelium and/or a fraenum breve. Paraphimosis is characterised by a retracted foreskin with the constrictive ring localised at the level of the sulcus, which prevents replacement of the foreskin over the glans.

3.1.4 *Management*

Conservative treatment is an option for primary phimosis. A corticoid ointment or cream (0.05-0.1%) can be administered twice a day over a period of 20-30 days with a success rate of > 90% [9-12] (LE: 1b). A recurrence rate of up to 17% can be expected [13]. This treatment has no side effects and the mean bloodspot

cortisol levels are not significantly different from an untreated group of patients [14] (LE: 1b). The hypothalamic pituitary-adrenal axis was not influenced by local corticoid treatment [15]. Agglutination of the foreskin does not respond to steroid treatment [11] (LE: 2).

Operative treatment of phimosis in children is dependent on the parents' preferences and can be plastic or radical circumcision after completion of the second year of life. Alternatively, the Shang Ring may be used especially in developing countries [16]. Plastic circumcision has the objective of achieving a wide foreskin circumference with full retractability, while the foreskin is preserved (dorsal incision, partial circumcision). However, this procedure carries the potential for recurrence of the phimosis [17]. In the same session, adhesions are released and an associated fraenum breve is corrected by fraenulotomy. Meatoplasty is added if necessary.

An absolute indication for circumcision is secondary phimosis. In primary phimosis, recurrent balanoposthitis and recurrent urinary tract infections (UTIs) in patients with urinary tract abnormalities are indications for intervention [18-21] (LE: 2b). Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [22] (LE: 2b). Simple ballooning of the foreskin during micturition is not a strict indication for circumcision.

Routine neonatal circumcision to prevent penile carcinoma is not indicated. A recent meta-analysis could not find any risk in uncircumcised patients without a history of phimosis [23]. Contraindications for circumcision are: an acute local infection and congenital anomalies of the penis, particularly hypospadias or buried penis, as the foreskin may be required for a reconstructive procedure [24, 25]. Circumcision can be performed in children with coagulopathy with 1-5% suffering complications (bleeding), if haemostatic agents or a diathermic knife are used [26, 27]. Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason and also taking into account epidemiological and social aspects [28-32] (LE: 1b).

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis. Injection of hyaluronidase beneath the narrow band or 20% mannitol may be helpful to release the foreskin [33, 34] (LE: 3-4). If this manoeuvre fails, a dorsal incision of the constrictive ring is required. Depending on the local findings, a circumcision is carried out immediately or can be performed in a second session.

3.1.5 **Follow-up**

Any surgery done on the prepuce requires an early follow-up of four to six weeks after surgery.

3.1.6 **Summary of evidence and recommendations for the management of phimosis**

Summary of evidence	LE
Treatment for phimosis usually starts after two years of age or according to parents' preference.	3
In primary phimosis, conservative treatment with a corticoid ointment or cream is a first line treatment with a success rate of more than 90%.	1b

Recommendations	LE	GR
Treat primary phimosis conservatively with a corticoid ointment or cream. Circumcision will also solve the problem if being considered.	1b	A
Do not delay treatment of primary phimosis in recurrent balanoposthitis and recurrent urinary tract infection (UTI) in patients with urinary tract abnormalities.	2b	A
Circumcision is indicated in secondary phimosis.	2b	A
Do not delay treatment in case of paraphimosis, this is an emergency situation. Perform a dorsal incision of the constrictive ring if manual reposition has failed.	3	B
Routine neonatal circumcision is not recommended to prevent penile carcinoma.	2b	B

3.2 **Management of undescended testes**

3.2.1 **Background**

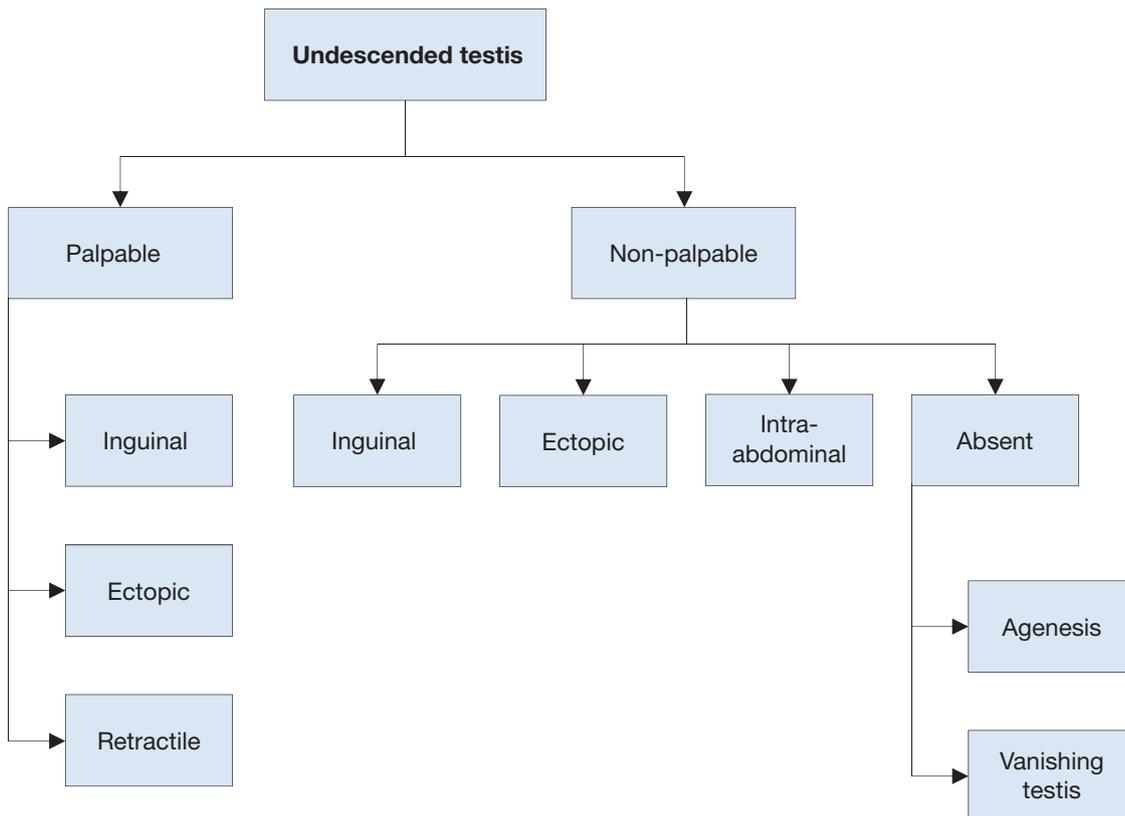
Cryptorchidism or undescended testis is one of the most common congenital malformations of male neonates. Incidence varies and depends on gestational age, affecting 1.0-4.6% of full-term and 1.1-45% of preterm neonates. Following spontaneous descent within the first months of life, nearly 1.0% of all full-term male infants still have undescended testes at one year of age [35]. This congenital malformation may affect both sides in up to 30% of cases [36]. In newborn cases with non-palpable or undescended testes on both sides and any sign of disorders of sex development (DSDs) like concomitant hypospadias, urgent endocrinological and genetic evaluation is required [37].

3.2.2 Classification

The term cryptorchidism is most often used synonymously for undescended testes. The most useful classification of undescended testes is distinguishing into palpable and non-palpable testes, and clinical management is decided by the location and presence of the testes (see Figure 1). Approximately 80% of all undescended testes are palpable [38]. Acquired undescended testes can be caused by entrapment after herniorrhaphy or spontaneously referred to as ascending testis.

Palpable testes include true undescended testes and ectopic testes. Non-palpable testes include intra-abdominal, inguinal, absent, and sometimes also some ectopic testes. Most importantly, the diagnosis of palpable or non-palpable testis needs to be confirmed once the child is under general anaesthesia, as this is the first step of any surgical procedure for undescended testes.

Figure 1: Classification of undescended testes



3.2.2.1 Palpable testes

Undescended testes

A true undescended testis is on its normal path of descent but is halted on its way down to the scrotum. Depending on the location, the testes may be palpable or not, as in the case of testes arrested in the inguinal canal.

Ectopic testes

If the position of a testis is outside its normal path of descent and outside the scrotum, the testis is considered to be ectopic. The most common aberrant position is in the superficial inguinal pouch. Sometimes an ectopic testis can be identified in a femoral, perineal, pubic, penile or even contralateral position. Usually, there is no possibility for an ectopic testis to descend spontaneously to the correct position; therefore, it requires surgical intervention. In addition, an ectopic testis might not be palpable due to its position.

Retractile testes

Retractile testes have completed their descent into a proper scrotal position but can be found again in a suprascrotal position along the path of their normal descent. This is due to an overactive cremasteric reflex [39]. Retractile testes can be easily manipulated down to the scrotum and remain there at least temporarily. They are typically normal in size and consistency. However, they may not be normal and should be monitored carefully since up to one-third can ascend and become undescended [40].

3.2.2.2 *Non-palpable testes*

Among the 20% of non-palpable testes, 50-60% are intra-abdominal, canalicular or peeping (right inside the internal inguinal ring). The remaining 20% are absent and 30% are atrophic or rudimentary.

Intra-abdominal testes

Intra-abdominal testes can be located in different positions, with most of them being found close to the internal inguinal ring. However, possible locations include the kidney, anterior abdominal wall, and retrovesical space. In the case of an open internal inguinal ring, the testis may be peeping into the inguinal canal.

Absent testes

Monorchidism can be identified in up to 4% of boys with undescended testes, and anorchidism (bilateral absence) in < 1%. Possible pathogenic mechanisms include testicular agenesis and atrophy after intrauterine torsion with the latter one most probably due to an in utero infarction of a normal testis by gonadal vessel torsion. The term vanishing testis is commonly used for this condition [41].

3.2.3 **Diagnostic evaluation**

History taking and physical examination are key in evaluating boys with undescended testes. Localisation studies using different imaging modalities are usually without any additional benefit.

3.2.3.1 *History*

Parents should be asked for maternal and paternal risk factors, including hormonal exposure and genetic or hormonal disorders. If the child has a history of previously descended testes this might be suggestive of testicular ascent [42]. Prior inguinal surgery is indicative of secondary undescended testes due to entrapment.

3.2.3.2 *Physical examination*

An undescended testis is pursued by carefully advancing the examining fingers along the inguinal canal towards the pubis region, perhaps with the help of lubricant. A possible inguinal testis can be felt to bounce under the fingers [43]. A non-palpable testis in the supine position may become palpable once the child is in a sitting or squatting position. If no testis can be identified along the normal path of descent, possible ectopic locations must be considered.

In case of unilateral non-palpable testis, the contralateral testis needs to be examined. Its size and location can have important prognostic implications. Any compensatory hypertrophy suggests testicular absence or atrophy [44]. Nevertheless, this does not preclude surgical exploration since the sign of compensatory hypertrophy is not specific enough [45].

In case of bilateral undescended testes and any evidence or sign of DSDs, such as genital ambiguity, or scrotal hyperpigmentation, further evaluation including endocrinological and genetic assessment becomes mandatory [46].

3.2.3.3 *Imaging studies*

Imaging studies cannot determine with certainty that a testis is present or not [47]. Ultrasound (US) lacks the diagnostic performance to detect the testis confidently or establish the absence of an intra-abdominal testis [48].

Consequently, the use of different imaging modalities, such as US or magnetic resonance imaging (MRI) [49], for undescended testes is limited and only recommended in specific and selected clinical scenarios (e.g., identification of Müllerian structures in cases with suspicion of DSDs) [50].

3.2.4 **Management**

Treatment should be started at the age of six months. After that age, undescended testes rarely descend [51]. Any kind of treatment leading to a scrotally positioned testis should be finished by twelve months, or eighteen months at the latest, because histological examination of undescended testes at that age has already revealed a progressive loss of germ cells and Leydig cells [52]. The early timing of treatment is also driven by the final adult results on spermatogenesis and hormone production, as well as on the risk of tumour development [53].

3.2.4.1 *Medical therapy*

Unfortunately, most of the studies on hormonal treatment have been of poor quality, with heterogeneous and mixed patient populations, testis location, schedules and dosages of hormonal administration. Additionally, long-term data are almost completely lacking.

Short-term side effects of hormonal treatment include increased scrotal erythema and pigmentation, and induction of pubic hair and penile growth. Some boys experience pain after intramuscular injection of human chorionic gonadotropin (hCG). All of these tend to regress after treatment cessation [54, 55].

3.2.4.1.1 Medical therapy for testicular descent

Hormonal therapy using hCG or gonadotropin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent, but has a maximum success rate of only 20% [56]. However, it must be taken into account that almost 20% of these descended testes have the risk of re-ascending later [54]. In general, success rates depend on testicular location. The higher the testis is located prior to therapy, the lower the success rate, suggesting that testicular position is an important determinant of success [55]. Some authors recommend combined hCG-GnRH treatment. Unfortunately, it is poorly documented and the treatment groups were diverse. Some studies reported successful descent in up to 38% of non-responders to monotherapy [57]. The Panel consensus is that endocrine treatment to achieve testicular descent is not recommended (LE: 4).

Human chorionic gonadotropin (hCG)

Human chorionic gonadotropin stimulates endogenous testosterone production and is administered by intramuscular injection. Several dose and administration schedules are reported. There is no proven difference between 1.5 IU and weight-based doses up to 3.0 IU every other day for fourteen days [58]. Similar response rates were achieved with 500 IU once weekly and 1.50 IU three times weekly [59]. However, there is evidence that dosing frequency might affect testicular descent rates. Fewer lower dose injections per week for five weeks seem to be superior to one higher dose every seven to ten days for three weeks with regard to testicular descent [60].

Gonadotropin-releasing hormone (GnRH)

Gonadotropin-releasing hormone analogues (e.g., buserelin and gonadorelin) are available as nasal sprays, thus avoiding painful intramuscular injections. A typical dosage regimen consists of 1.2 mg per day in three divided doses, for four weeks. Success rates are wide ranging, from 9 to 60%, due to multiple treatment strategies and heterogeneous patient populations [61].

3.2.4.1.2 Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [61, 62] and therefore serve as an additional tool to orchidopexy. There is no difference in treatment with GnRH before (neo-adjuvant) or after (adjuvant) surgical orchidolysis and orchidopexy in terms of increasing fertility index, which may be a predictor for fertility later in life [63]. It is still unknown whether this effect on testicular histology persists into adulthood but it has been shown that men who were treated in childhood with buserelin had better semen analyses compared with men who had childhood orchidopexy alone or placebo treatment [64].

It is reported that hCG treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells, including acute inflammatory changes in the testes and reduced testicular volume in adulthood [65].

Identification of specific subgroups of boys with undescended testes who would benefit from such an approach using hormones is difficult. Since these important data on specific groups as well as additional support on the long-term effects are still lacking, the Nordic consensus does not recommend hormonal therapy [66]. The Panel consensus recommends endocrine treatment with GnRH analogues in a dosage described above for boys with bilateral undescended testes to preserve the fertility potential (LE: 4, GR: C).

3.2.4.2 Surgical therapy

If a testis has not concluded its descent at the age of six months (corrected for gestational age), and since spontaneous testicular descent is unlikely to occur after that age, surgery should be performed within the subsequent year, and by age eighteen months at the latest [52]. In addition, early orchidopexy can be followed by partial catch-up testicular growth, which is not the case in delayed surgery [67]. All these findings recommend performing early orchidopexy between the ages of six and twelve months [51].

3.2.4.2.1 Palpable testes

Surgery for palpable testes includes orchidofunicolysis and orchidopexy, either via an inguinal or scrotal approach. The latter approach is mainly reserved for low-positioned, undescended testes, with the pros and cons of each method being weighed against each other [68].

3.2.4.2.1.1 Inguinal orchidopexy

Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% [69]. Important steps include mobilisation of the testis and spermatic cord to the level of the internal inguinal ring, with dissection and division of all cremasteric fibres, to prevent secondary retraction and detachment of the gubernaculum testis. The patent processus vaginalis needs to be ligated proximally at the level of the internal ring, because an unidentified or inadequately repaired patent processus vaginalis is an important factor leading to failure of orchidopexy [70]. Any additional pathology has to be taken care of, such as removal of an appendix testis

(hydatid of Morgagni). At this moment the size of the testis can be measured and the connection of the epididymis to the testis can be judged and described in the protocol. Some boys have a significant dissociation between testis and epididymis which is prognostically bad for fertility. Finally, the mobilised testicle needs to be placed in a sub-dartos pouch within the hemi-scrotum without any tension. In case the length achieved using the above-mentioned technique is still inadequate, the Prentiss manoeuvre, which consists of dividing the inferior epigastric vessels and transposing the spermatic cord medially, in order to provide a straight course to the scrotum, might be an option [71]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [72]. Lymph drainage of a testis that has undergone surgery for orchidopexy may have changed from high retroperitoneal drainage to iliac and inguinal drainage, which might become important in the event of later malignancy [73].

3.2.4.2.1.2 Scrotal orchidopexy

Low-positioned, palpable undescended testis can be fixed through a scrotal incision including division of the gubernaculum, and the processus vaginalis needs to be probed to check for patency [74]. Otherwise, fixation in the scrotum is carried out correspondingly to the inguinal approach. In up to 20% of cases, an inguinal incision will be compulsory to correct an associated inguinal hernia [75]. Any testicular or epididymal appendages can be easily identified and removed. A systematic review shows that the overall success rates ranged from 88 to 100%, with rates of recurrence and post-operative testicular atrophy or hypotrophy < 1% [68].

3.2.4.2.2 Non-palpable testes

For non-palpable testes, surgery must clearly determine whether a testis is present or not [76]. If a testis is found, the decision has to be made to remove it or bring it down to the scrotum. An important step in surgery is a thorough re-examination once the boy is under general anaesthesia, since a previously non-palpable testis might be identifiable and subsequently change the surgical approach to standard inguinal orchidopexy, as described above. Otherwise, the easiest and most accurate way to locate an intra-abdominal testis is diagnostic laparoscopy [77]. Subsequent removal or orchidolysis and orchidopexy can be carried out using the same approach to achieve the therapeutic aims [78]. Some tend to start with inguinal surgical exploration, with possible laparoscopy during the procedure [79]. If an ipsilateral scrotal nubbin is suspected, and contralateral compensatory testicular hypertrophy is present, a scrotal incision with removal of the nubbin, thus confirming the vanishing testis, is an option avoiding the need for laparoscopy [80].

During laparoscopy for non-palpable testes, possible anatomical findings include spermatic vessels entering the inguinal canal (40%), an intra-abdominal (40%) or peeping (10%) testis, or blind-ending spermatic vessels confirming vanishing testis (10%) [81].

In case of a vanishing testis, the procedure is finished once blind-ending spermatic vessels are clearly identified. If the vessels enter the inguinal canal, one may find an atrophic testis upon inguinal exploration or a healthy testis that needs to undergo standard orchidopexy [82]. A peeping testis can be placed down in the scrotum laparoscopically or via an inguinal incision [83]. Placement of an intra-abdominal testis can sometimes be a surgical challenge. Usually, testes lying > 2 cm above the internal inguinal ring may not reach the scrotum without division of the testicular vessels [84]. Under such circumstances, a Fowler-Stephens orchidopexy may be an option [85] (see Figure 2).

Proximal cutting and transection of the testicular vessels, with conservation of the collateral arterial blood supply, via the deferential artery and cremasteric vessels comprise the key features of the Fowler-Stephens procedure. Recently, a modification with low spermatic vessel ligation has gained popularity, allowing blood supply from the testicular artery to the deferential artery. An additional advantage is the position of the peritoneal incision, leading to a longer structure, to ease later scrotal placement [86]. Due to the nature of these approaches the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [87]. The testicular survival rate in the one-stage Fowler-Stephens technique varies between 50 and 60%, with success rates increasing up to 90% for the two-stage procedure [88]. The advantages of two-stage orchidopexy, with the second part done usually six months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility [89]. In addition preservation of the gubernaculum may also decrease the chance of testicular atrophy [90].

An alternative might be microsurgical auto-transplantation, which has a success rate of up to 90%. However, this approach requires skilled and experienced surgeons and is performed in a limited number of centres [91].

3.2.4.2.3 Complications of surgical therapy

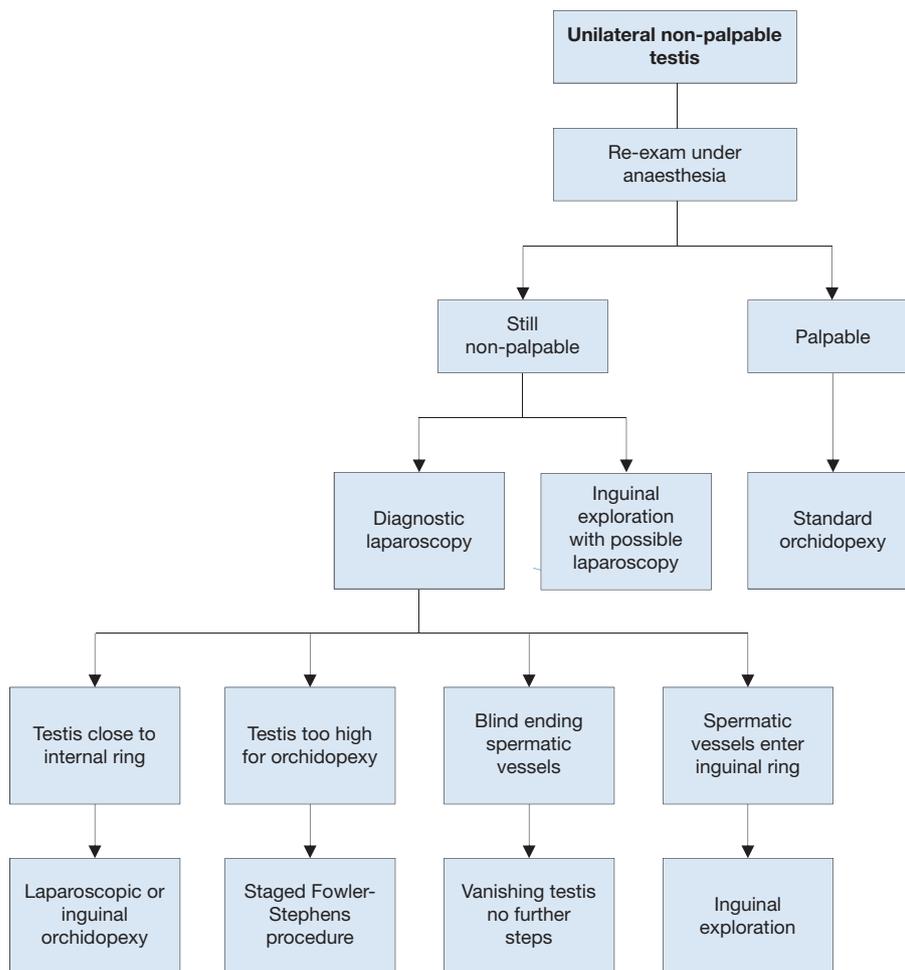
Surgical complications are usually uncommon, with testicular atrophy being the most serious. A systematic review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for one-stage Fowler-Stephens procedure, and 8.2% for the two-stage approach [92]. Other rare complications comprise testicular ascent and vas deferens injury besides local wound infection, dehiscence, and haematoma.

3.2.4.2.4 Surgical therapy for undescended testes after puberty

A recent study on 51 men diagnosed with inguinal unilateral undescended testis and a normal contralateral one, with no history of any previous therapy, demonstrated a wide range of changes upon histological evaluation. Nearly half of the study population still had significant germ cell activity at different maturation levels. Importantly, the incidence of intratubular germ cell neoplasia was 2% [93].

The Panel consensus recommends orchiectomy in post-pubertal boys with an undescended testis and a normal contralateral one in a scrotal position.

Figure 2: Treatment of unilateral non-palpable undescended testes



3.2.5 Undescended testes and fertility

The association of undescended testes with compromised fertility [94] is extensively discussed in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [95], Leydig cell diminution and testicular fibrosis [96].

Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as those with bilateral descended testes. Boys with bilateral undescended testes suffer both, lower fertility and paternity rates. Fertility rate is the number of offspring born per mating pair, individual of population, whereas paternity reflects the actual potential of fatherhood [97]. The age at which surgical intervention for an undescended testis happens seems to be an important predictive factor for fertility later in life. Endocrinological studies revealed higher inhibin-B and lower follicle-stimulating hormone (FSH) levels in men who underwent orchidopexy at age two years compared to individuals who had surgery later, which is indicative of a benefit of earlier orchidopexy [98]. In addition, others demonstrated a relation between undescended testes and

increased loss of germ cells and Leydig cells, which is also suggestive of prompt orchidopexy being a significant factor for fertility preservation [99].

Outcome studies for untreated bilateral undescended testes revealed that 100% are oligospermic and 75% azoospermic. Among those successfully treated for bilateral undescended testes, 75% still remain oligospermic and 42% azoospermic [96].

In summary, regarding preservation of fertility potential, early surgical correction of undescended testes is highly recommended before twelve months of age, and by eighteen months at the latest [52].

3.2.6 **Undescended testes and malignancy**

Boys who are treated for an undescended testis have an increased risk of developing testicular malignancy. Screening and self-examination both during and after puberty is therefore recommended [100]. A Swedish study, with a cohort of almost 17,000 men (56 developed a testicular tumour) who were treated surgically for undescended testes and followed for 210,000 person-years, showed that management of undescended testes before the onset of puberty decreased the risk of testicular cancer. The relative risk of testicular cancer among those who underwent orchidopexy before thirteen years of age was 2.2 compared to the Swedish general population; this increased to 5.4 for those treated after thirteen years of age [101].

A systematic review and meta-analysis of the literature have also concluded that pre-pubertal orchidopexy may reduce the risk of testicular cancer and that early surgical intervention is indicated in boys with undescended testes [102].

3.2.7 **Summary of evidence and recommendations for the management of undescended testes**

Summary of evidence	LE
An undescended testis justifies treatment early in life to avoid loss of spermatogenic potential.	2a
A failed or delayed orchidopexy may increase the risk of testicular malignancy later in life.	2a
The earlier the treatment, the lower the risk of impaired fertility and testicular cancer.	2a
In unilateral undescended testis, fertility rate is reduced whereas paternity rate is not.	1b
In bilateral undescended testes, fertility and paternity rates are impaired.	1b
The treatment of choice for undescended testis is surgical replacement in the scrotum.	1b
The palpable testis is usually treated surgically using an inguinal approach.	2b
The non-palpable testis is most commonly approached laparoscopically.	2b
There is no consensus on the use of hormonal treatment.	2b

Recommendations	LE	GR
Boys with retractile testes do not need medical or surgical treatment, but ensure close follow-up until puberty.	2a	A
Perform surgical orchidolysis and orchidopexy before the age of twelve months, and by eighteen months at the latest.	2b	B
Evaluate male neonates with bilateral non-palpable testes for possible disorders of sex development (DSD).	1b	A
In case of non-palpable testes and no evidence of DSDs, laparoscopy is recommended because of its excellent sensitivity and specificity in identifying an intra-abdominal testis, as well as the possibility for subsequent treatment in the same session.	1a	A
Do not routinely offer hormonal therapy, either in an adjuvant or neo-adjuvant setting. Patients have to be evaluated on an individual basis.	2a	C
In case of bilateral undescended testes, offer endocrine treatment.	4	C
For an undescended testis in a post-pubertal boy or older, with a normal contralateral testis, discuss removal with the patient/parents because of the theoretical risk of a later malignancy.	3	B

3.3 **Hydrocele**

3.3.1 **Epidemiology, aetiology and pathophysiology**

Hydrocele is defined as a collection of fluid between the parietal and visceral layers of the tunica vaginalis [103]. Pathogenesis of primary hydrocele is based on patency of processus vaginalis in contrast with secondary hydrocele. Incomplete obliteration of the processus vaginalis peritonei results in formation of various types of communicating hydrocele; a large open processus vaginalis allowing passage of abdominal viscera results in clinical hernia [104]. The exact time of spontaneous closure of the processus vaginalis is not known. It persists in approximately 80-94% of newborns and in 20% of adults [105]. If complete obliteration

of the processus vaginalis occurs with patency of midportion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are also encountered in newborns [106]. Non-communicating hydroceles, based on an imbalance between the secretion and re-absorption of this fluid, are found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation or may appear as a recurrence after primary repair of a communicating or non-communicating hydrocele.

3.3.2 **Diagnostic evaluation**

The classic description of a communicating hydrocele is that of a hydrocele that vacillates in size, and is usually related to ambulation. It may be diagnosed by history and physical investigation. Transillumination of the scrotum provides the diagnosis in the majority of cases, keeping in mind that fluid-filled intestine and some pre-pubertal tumours may transilluminate as well [107, 108]. If the diagnosis is that of a hydrocele, there will be no history of reducibility and no associated symptoms; the swelling is translucent, smooth and usually nontender. If there are any doubts about the character of an intrascrotal mass, scrotal US should be performed and has nearly 100% sensitivity in detecting intrascrotal lesions. Doppler US studies help to distinguish hydroceles from varicocele and testicular torsion, although these conditions may also be accompanied by a hydrocele.

3.3.3 **Management**

In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months because of the tendency for spontaneous resolution [109] (LE: 2). Little risk is taken by initial observation as progression to hernia is rare and does not result in incarceration [109]. Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology [110, 111] (LE: 2). Persistence of a simple scrotal hydrocele beyond twelve months of age may be an indication for surgical correction. There is no evidence that this type of hydrocele risks testicular damage. The natural history of hydrocele is poorly documented beyond the age of two years and according to a systematic review there is no good evidence to support current practice. Delaying surgery may reduce the number of procedures necessary without increasing morbidity [112].

The question of contralateral disease should be addressed by both history and physical examination at the time of initial consultation (LE: 2) [113]. In late-onset hydrocele, suggestive of a non-communicating hydrocele, there is a reasonable chance of spontaneous resolution (75%) and expectant management of six to nine months is recommended [114]. In the paediatric age group, the operation consists of ligation of patent processus vaginalis via inguinal incision and the distal stump is left open, whereas in hydrocele of the cord the cystic mass is excised or unroofed [103, 108, 110] (LE: 4). In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low (0.3%) (LE: 3). Sclerosing agents should not be used because of the risk of chemical peritonitis in communicating processus vaginalis peritonei [108, 110] (LE: 4). The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele.

3.3.4 **Summary of evidence and recommendations for the management of hydrocele**

Summary of evidence	LE
In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months due to the tendency for spontaneous resolution. Little risk is taken by initial observation as progression to hernia is rare.	2a
In the paediatric age group, an operation would generally involve ligation of the patent processus vaginalis via inguinal incision.	4

Recommendations	LE	GR
In the majority of infants, observe hydrocele for twelve months prior to considering surgical treatment.	2a	B
Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	2b	B
Perform a scrotal ultrasound in case of doubt about the character of an intrascrotal mass.	4	C
Do not use sclerosing agents because of the risk for chemical peritonitis.	4	C

3.4 Acute scrotum

3.4.1 *Epidemiology, aetiology and pathophysiology*

Acute scrotum is a paediatric urological emergency, most commonly caused by torsion of the testis or appendix testis, or epididymitis/epididymo-orchitis [115-120]. Other causes of acute scrotal pain are idiopathic scrotal oedema, mumps orchitis, varicocele, scrotal haematoma, incarcerated hernia, appendicitis or systemic disease (e.g. Henoch-Schönlein purpura) [121-133]. Trauma can also be a cause of acute scrotum as it can relate to post-traumatic haematomas, testicular contusion, rupture dislocation or torsion [134-139]. Scrotal fat necrosis has also been reported to be an uncommon cause of mild-to-moderate scrotal pain in pre-pubertal overweight boys after exposure to cold [140].

In this chapter testicular torsion and epididymitis is discussed, while recurrent epididymitis is discussed in the chapter dealing with infections. Torsion of the testis occurs most often in the neonatal period and around puberty, whereas torsion of the appendix testes occurs over a wider age range.

Epididymitis affects two age groups: less than one year and twelve to fifteen years [118, 141, 142]. One study predicted the annual incidence of epididymitis around 1.2 per 1,000 children [143]. Perinatal torsion of the testis most often occurs prenatally. Bilateral torsion comprises 11-21% of all perinatal cases [144]. Most cases are extravaginal in contrast to the usual intravaginal torsion, which occurs during puberty.

3.4.2 *Diagnostic evaluation*

Patients usually present with scrotal pain, except in neonatal torsion. The sudden onset of invalidating pain in combination with vomiting is typical for torsion of the testis or appendix testes [145, 146].

In general the duration of symptoms is shorter in testicular torsion (69% present within twelve hours) and torsion of the appendix testes (62%) compared to epididymitis (31%) [117, 118, 142].

In the early phase, location of the pain can lead to diagnosis. Patients with acute epididymitis experience a tender epididymis, whereas patients with testicular torsion are more likely to have a tender testicle, and patients with torsion of the appendix testis feel isolated tenderness of the superior pole of the testis [142].

An abnormal (horizontal) position of the testis is more frequent in testicular torsion than epididymitis [117]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [141, 146] (LE:3). Elevation of the scrotum may reduce complaints in epididymitis, but not in testicular torsion.

Fever occurs more often in epididymitis (11-19%). The classical sign of a “blue dot” was found only in 10-23% of patients with torsion of the appendix testis [116, 117, 141, 147]. In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [115-120, 141, 147].

A positive urine culture is only found in a few patients with epididymitis [119, 141, 147, 148]. It should be remembered that a normal urinalysis does not exclude epididymitis. Similarly, an abnormal urinalysis does not exclude testicular torsion.

Doppler US is useful to evaluate acute scrotum, with 63.6-100% sensitivity and 97-100% specificity, and a positive predictive value of 100% and negative predictive value of 97.5% [149-154] (LE: 3). The use of Doppler US may reduce the number of patients with acute scrotum undergoing scrotal exploration, but it is operator-dependent and can be difficult to perform in pre-pubertal patients [151, 155]. It may also show a misleading arterial flow in the early phases of torsion and in partial or intermittent torsion. Of key importance, persistent arterial flow does not exclude testicular torsion. In a multicentre study of 208 boys with torsion of the testis, 24% had normal or increased testicular vascularisation [151]. A comparison with the other side should always be done

Better results were reported using high-resolution US (HRUS) for direct visualisation of the spermatic cord twist with a sensitivity of 97.3% and specificity of 99% [151, 156] (LE: 2).

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to US [157-160]. These investigations may be used when diagnosis is less likely and if torsion of the testis still cannot be excluded from history and physical examination. This should be done without inordinate delays for emergency intervention [147].

The diagnosis of acute epididymitis in boys is mainly based on clinical judgement and adjunctive investigation. However, it should be remembered that findings of secondary inflammatory changes in the absence of evidence of an extra-testicular nodule by Doppler US might suggest an erroneous diagnosis of epididymitis in children with torsion of the appendix testes [161]. Pre-pubertal boys with acute epididymitis have an incidence of underlying urogenital anomalies of 25-27.6%. Complete urological evaluation in all children with acute epididymitis is still debatable [119, 141, 143].

3.4.3 **Management**

3.4.3.1 *Epididymitis*

In pre-pubertal boys, the aetiology is usually unclear, with an underlying pathology in about 25%. A urine culture is usually negative, and unlike in older boys, a sexually transmitted disease is very rare.

Antibiotic treatment, although often started, is not indicated in most cases unless urinalysis and urine culture show a bacterial infection [143, 162]. Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required [163].

3.4.3.2 *Testicular torsion*

Manual detorsion of the testis is done without anaesthesia. It should initially be done by outwards rotation of the testis unless the pain increases or if there is obvious resistance. Success is defined as the immediate relief of all symptoms and normal findings at physical examination [164] (LE: 3; GR: C). Doppler US may be used for guidance [165]. Bilateral orchiopexy is still required after successful detorsion. This should not be done as an elective procedure, but rather immediately following detorsion. One study reported residual torsion during exploration in 17 out of 53 patients, including eleven patients who had reported pain relief after manual detorsion [164, 166].

Torsion of the appendix testis can be managed non-operatively with the use of anti-inflammatory analgesics (LE: 4). During the six-week follow-up, clinically and with US, no testicular atrophy was revealed. Surgical exploration is done in equivocal cases and in patients with persistent pain [154].

3.4.3.3 *Surgical treatment*

Testicular torsion is an urgent condition, which requires prompt surgical treatment. The two most important determinants of early salvage rate of the testis are the time between onset of symptoms and detorsion, and the degree of cord twisting [167]. Severe testicular atrophy occurred after torsion for as little as four hours when the turn was $> 360^\circ$. In cases of incomplete torsion ($180-360^\circ$), with symptom duration up to twelve hours, no atrophy was observed. However, an absent or severely atrophied testis was found in all cases of torsion $> 360^\circ$ and symptom duration > 24 hours [168].

Early surgical intervention with detorsion (mean torsion time less than thirteen hours) was found to preserve fertility [169]. Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 hours of symptom onset. In patients with testicular torsion > 24 hours, semi-elective exploration is necessary [167, 168] (LE: 3). There is still controversy on whether to carry out detorsion and to preserve the ipsilateral testis, or to perform an orchiectomy, in order to preserve contralateral function and fertility after testicular torsion of long duration (> 24 hours).

A study found that sperm quality was preserved after orchiectomy and orchidopexy in comparison to normal control men, although orchiectomy resulted in better sperm morphology [170].

During exploration, fixation of the contralateral testis is also performed. Recurrence after orchidopexy is rare (4.5%) and may occur several years later. There is no consensus recommendation about the preferred type of fixation and suture material [171]. Incision of the tunica albuginea with tunica vaginalis graft to prevent or treat compartment syndrome has also been suggested [172].

External cooling before exploration and several medical treatments seem effective in reducing ischaemia-reperfusion injury and preserving the viability of the torsed and the contralateral testis [173-177]. It is good clinical practice to perform fixation also of the contralateral testis in prenatal and neonatal torsion, although there is no literature to support this and to remove an atrophied testicle.

3.4.4 **Follow-up**

Patients require follow-up mainly for fertility issues and hormonal consequences. Despite timely and adequate detorsion and fixation of the testicle, up to half of the patients may develop testicular atrophy, even when intra-operatively assessed as viable, and should be counseled accordingly [178].

3.4.4.1 *Fertility*

The results vary and are conflicting. In one study, unilateral torsion of the testis seriously intervened with subsequent spermatogenesis in about 50% of the patients and produced borderline impairment in another 20% [167]. Although, 30% of affected testicles with mumps orchitis show a degree of atrophy, long-term outcome in terms of fertility is not conclusive [179].

A recent study showed a normal pregnancy rate after unilateral testicular torsion, with no difference between the patients undergoing orchidopexy and those after orchiectomy [180].

3.4.4.2 Subfertility

Subfertility is found in 36-39% of patients after torsion. Semen analysis may be normal in only 5-50% in long-term follow-up [167]. Early surgical intervention (mean torsion time less than thirteen hours) with detorsion was found to preserve fertility, but a prolonged torsion period (mean 70 hours) followed by orchiectomy jeopardised fertility [169].

Subfertility and infertility are consequences of direct injury to the testis after the torsion. This is caused by the cut-off of blood supply, but also by post-ischæmia-reperfusion injury that is caused after the detorsion when oxygen-derived free radicals are rapidly circulated within the testicular parenchyma [167].

3.4.4.3 Androgen levels

Even though the levels of FSH, luteinising hormone (LH) and testosterone are higher in patients after testicular torsion compared to normal controls, endocrine testicular function remains in the normal range after testicular torsion [170].

3.4.4.4 Unanswered questions

Although testicular torsion is a common problem the mechanism of neonatal and prenatal torsion is still not exactly known and whether fixation of the contralateral testicle in these cases is really necessary. The influence of an atrophied testicle on fertility is also unclear.

3.4.5 Summary of evidence and recommendations for the management of acute scrotum in children

Summary of evidence	LE
Diagnosis of testicular torsion is based on presentation and physical exam.	
Doppler US is an effective imaging tool to evaluate acute scrotum and comparable to scintigraphy and dynamic contrast-enhanced subtraction MRI.	2a
Neonates with acute scrotum should be treated as surgical emergencies.	3

Recommendations	LE	GR
Do not delay intervention since testicular torsion is a paediatric urological emergency.	3	A
In neonates, also explore the contralateral scrotum.	3	C
Base the clinical decision on physical examination. The use of Doppler ultrasound to evaluate acute scrotum is useful, but this should not delay the intervention.	2a	B
Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	3	B
Perform urgent surgical exploration in all cases of testicular torsion within 24 hours of symptom onset. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	3	C

3.5 Hypospadias

3.5.1 Epidemiology, aetiology and pathophysiology

3.5.1.1 Epidemiology

The total prevalence of hypospadias in Europe is 18.6 new cases per 10,000 births (5.1-36.8) according to the recent EUROCAT registry-based study. This incidence was stable over the period of 2001 to 2010 [181, 182]. The mean worldwide prevalence of hypospadias according to an extended systematic literature review varies: Europe 19.9 (range: 1-464), North America 34.2 (6-129.8), South America 5.2 (2.8-110), Asia 0.6-69, Africa 5.9 (1.9-110), and Australia 17.1-34.8. There are conflicting data on the recent trends of prevalence - different trends in Europe and increasing in the USA [183, 184].

3.5.2 Risk factors

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [181, 182] (LE: 2b). Interactions between genetic and environmental factors may help explain non-replication in genetic studies of hypospadias. Single nucleotide polymorphisms seemed to influence hypospadias risk only in exposed cases [182, 185] (LE: 2b).

- An additional family member with hypospadias is found in 7% of families, but this is more predominant in anterior and middle forms [185-188].
- Endocrine disorders can be detected in rare cases.
- Babies with a low birth weight have a higher risk of hypospadias [185-188].

- Over the last 25 years, a significant increase in the incidence of hypospadias has been found.
- Endocrines disruptors are one component of a multi-factorial model for hypospadias.
- The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in offspring, but their use after conception increased the risk of middle and posterior hypospadias [187-190] (LE: 2a).

3.5.3 **Classification systems**

Hypospadias are usually classified based on the anatomical location of the proximally displaced urethral orifice:

- distal-anterior hypospadias (located on the glans or distal shaft of the penis and the most common type of hypospadias);
- intermediate-middle (penile);
- proximal-posterior (penoscrotal, scrotal, perineal).

The pathology may be different after skin release and should be reclassified accordingly. Anatomical location of meatus may not always be enough to explain the severity and the complex nature of this pathology. Therefore, a simple classification related to severity of the problem, which takes into account penile length, glans size, shape, urethral plate quality and penile curvature is commonly used. In that classification there are 2 types:

- mild hypospadias (glanular or penile isolated hypospadias without associated chordee, micropenis or scrotal anomaly);
- severe hypospadias (penoscrotal, perineal hypospadias with associated chordee and scrotal anomalies).

3.5.4 **Diagnostic evaluation**

Most hypospadias patients are easily diagnosed at birth (except for the megameatus intact prepuce variant).

Diagnosis includes a description of the local findings:

- position, shape and width of the orifice;
- presence of atretic urethra and division of corpus spongiosum;
- appearance of the preputial hood and scrotum;
- size of the penis;
- curvature of the penis on erection.

The diagnostic evaluation also includes an assessment of associated anomalies, which are:

- cryptorchidism (in up to 10% of cases of hypospadias);
- open processus vaginalis or inguinal hernia (in 9-15%).

Severe hypospadias with unilaterally or bilaterally impalpable testis, or with ambiguous genitalia, requires a complete genetic and endocrine work-up immediately after birth to exclude DSD, especially congenital adrenal hyperplasia.

Urine trickling and ballooning of the urethra requires exclusion of meatal stenosis. The relationship between the severity of the hypospadias and associated anomalies of the upper- or lower urinary tract were not confirmed [191] (LE: 3).

3.5.5 **Management**

3.5.5.1 *Indication for reconstruction and therapeutic objectives*

Differentiation between functionally necessary and aesthetically feasible operative procedures is important for therapeutic decision making.

The functional indications for surgery are:

- proximally located (ectopic) meatus;
- ventrally deflected or spraying urinary stream;
- meatal stenosis;
- curved penis.

The cosmetic indications, which are strongly linked to the psychology of the parent or future patient's psychology, are:

- abnormally located meatus;
- cleft glans;
- rotated penis with abnormal cutaneous raphe;
- preputial hood;
- penoscrotal transposition;
- split scrotum.

As all surgical procedures carry the risk of complications, thorough pre-operative counselling of the parents is crucial.

To achieve an overall acceptable functional and cosmetic outcome, the penile curvature must be corrected and a neo-urethra of an adequate size with opening on the glans formed with proper skin coverage of the penile shaft [192] (LE: 4) (Figure 1). The use of magnifying spectacles and fine synthetic absorbable suture materials (6.0-7.0) are required. As in any penile surgery, exceptional prudence should be adopted with the use of cautery. Bipolar cautery is recommended. Knowledge of a variety of surgical reconstructive techniques, wound care and post-operative treatment are essential for a satisfactory outcome.

3.5.5.2 *Pre-operative hormonal treatment*

Pre-operative hormonal treatment with local or parenteral application of testosterone, dihydrotestosterone or beta-chorionic gonadotropin is usually limited to patients with proximal hypospadias, a small appearing penis, reduced glans circumference or reduced urethral plate [190, 193, 194]. It leads to significant enlargement of the glans and shaft of the penis (LE: 1b).

Pre-operative testosterone administration is most often well tolerated. Transient side effects on child's behaviour, appearance of pubic hair, increased erections and peri-operative bleeding have been reported, but no persistent side effects related to hormonal stimulation have been reported in the literature. There is also no evidence about possible effects on bone maturation [194, 195].

3.5.5.3 *Age at surgery*

The age at surgery for primary hypospadias repair is usually 6-18 (24) months [192, 196, 197] (LE: 3). Age at surgery is not a risk factor for urethroplasty complication in pre-pubertal tubularised incised plate urethroplasty (TIP) repair [196] (LE: 2b). Complication rate after primary TIP repair was 2.5 times higher in adults than in the paediatric group according to a recent prospective controlled study [198] (LE:2a).

3.5.5.4 *Penile curvature*

If present, penile curvature is often released by degloving the penis (skin chordee) and by excision of the connective tissue of the genuine chordee on the ventral aspect of the penis in up to 70% [199]. The urethral plate has well vascularised connective tissue and does not cause curvature in most cases [200, 201]. The residual curvature is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal midline plication or orthoplasty (modification of the Nesbit plication with or without elevation of the neurovascular bundle). In more severe curvature (> 45°), which is often combined with a short urethral plate requiring transection, ventral penile lengthening is recommended to prevent shortening of the penis. This consists of a ventral transverse incision of tunica albuginea extending from the 3 to 9 o'clock position patched with tunica vaginalis flap or graft, or in several short ventral corporotomies without grafting (LE: 2b) [202]. After the ventral lengthening, a shorter dorsal midline plication is usually added.

According to a retrospective study, dorsal plication remained significantly associated with recurrent ventral curvature independently of the other factors. Ventral corporeal grafting for severe penile curvature gives good long-term results and safety profiles for erectile function [203] (LE: 2b).

3.5.5.5 *Urethral reconstruction*

The mainstay of hypospadias repair is preservation of the well-vascularised urethral plate and its use for urethral reconstruction has become standard practice in hypospadias repair [201]. Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection [202] (LE: 2b).

If the urethral plate is wide, it can be tubularised following the Thiersch-Duplay technique. If the plate is too narrow to be simply tubularised, it is recommended relaxing the plate by a midline incision and its subsequent tubularisation according to the Snodgrass-Orkiszewski TIP technique. This technique has become treatment of choice in distal and mid-penile hypospadias [204-208]. If the incision of the plate is deep, it is recommended covering the raw surface with inner preputial (or buccal) inlay graft in primary and secondary repairs [209]. This also enables extension of the incision beyond the end of the plate to prevent meatal stenosis [210, 211] (LE 2a).

For distal forms of hypospadias, a range of other techniques is available (e.g. Mathieu, urethral advancement) [212] (LE: 2b). The TIP technique has become an option for proximal hypospadias as well [204-208]. However, urethral plate elevation and urethral mobilisation should not be combined with TIP repair because it results in focal devascularisation of the neourethra with symptomatic stricture development [213] (LE: 2b). The onlay technique using a preputial island flap is a standard repair, preferred in proximal hypospadias, if a plate is unhealthy or too narrow [199]. An onlay preputial graft is an option for single-stage repair [214] (LE: 2b).

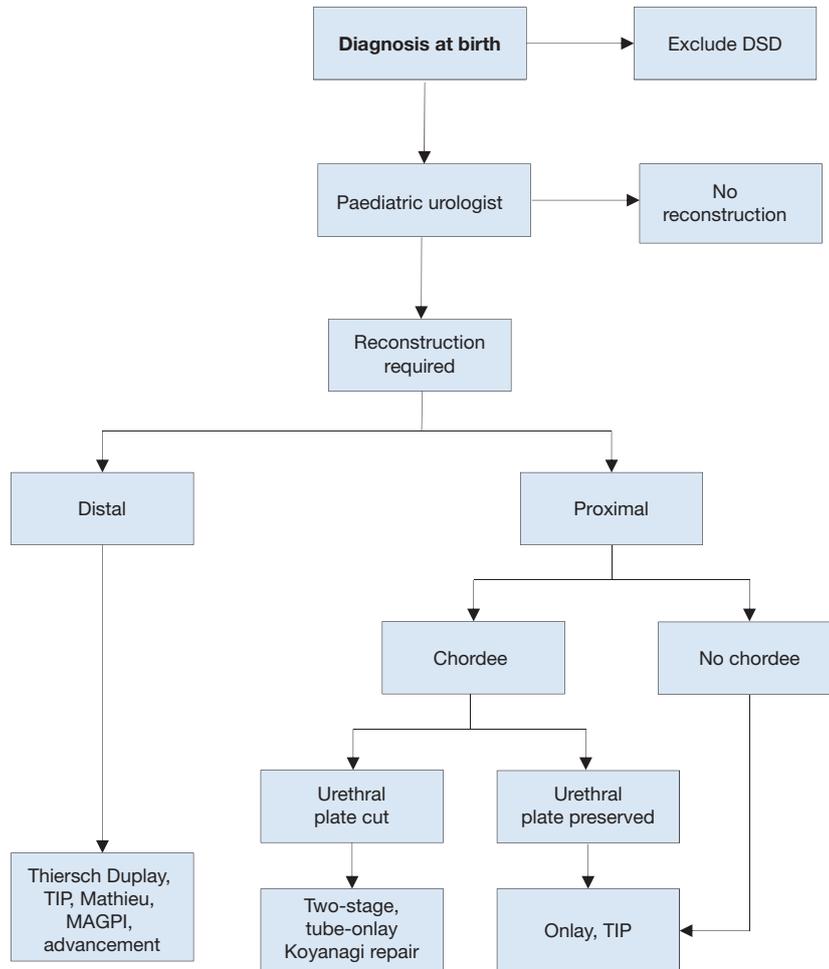
If the continuity of the urethral plate cannot be preserved, single or two-stage repairs are used. For the former, a modification of the tubularised flap (Duckett tube), such as a tube-onlay or an inlay-onlay flap, or onlay

flap on albuginea are used to prevent urethral stricture [215-217] (LE: 3); alternatively the Koyanagi-Hayashi technique is used [218-221]. The two-stage procedure has become preferable over the past few years because of lower recurrence of ventral curvature and more favourable results with variable long-term complication rate [211, 217, 222-226].

3.5.5.6 Re-do hypospadias repairs

For re-do hypospadias repairs, no definitive guidelines can be given. All the above-mentioned procedures are used in different ways and are often modified according to the individual findings and needs of the patient.

Figure 3: Algorithm for the management of hypospadias



DSD = disorders of sex development; GAP = glans approximation procedure; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

3.5.5.7 Penile reconstruction following formation of the neourethra.

Following formation of the neo-urethra, the procedure is completed by glansplasty and by reconstruction of the penile skin. If there is a shortage of skin covering, the preputial double-face technique or placement of the suture line into the scrotum according to Cecil-Michalowski is used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. Preputial reconstruction carries a risk of specific complications but does not seem to increase the risk of urethroplasty complications [227]. In the TIP repair, the use of a preputial dartos flap reduces the fistula rate [204, 205] (LE: 2b).

3.5.5.8 Urine drainage and wound dressing

Urine is drained transurethrally (eg. dripping stent) or with a suprapubic tube. No drainage after distal hypospadias repair is another option [228, 229]. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures [228] (LE: 4). Post-operative prophylaxis after hypospadias repair is controversial [230, 231] (LE: 2b). There is no consensus on duration of stenting and dressing.

3.5.5.9 Outcome

Some studies have tried to determine risk factors for complications after hypospadias repair. An analysis of prospectively collected data found glans size (width < 14 mm), proximal meatal location and re-operation as independent risk factors for urethral complication [228, 232]. Low surgeon volume independently increases the risk of fistula, stricture or diverticulum repair [228, 233] (LE: 3).

A meta-analysis of complication rates of TIP repair found lower complication rate and incidence of re-operations in primary distal repairs (in 4.5%) than in primary proximal repairs (in 12.2%) and in secondary repair (in 23.3%) [204-208, 228]. One should expect a predictable outcome with complication rates below 10% in distal hypospadias (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) [233, 234]. A similar incidence of fistula (3.4-3.6%) can be expected after the Mathieu and TIP repairs of distal hypospadias [208, 235, 236].

The complication rate of TIP and onlay repairs of primary severe hypospadias is similar, 24% and 27%, respectively. It is higher in free graft and in preputial island tube urethroplasty [199]. The complication rate of single-stage Koyanagi and Hayashi modification repairs goes up 61%, according to a comparative study [220, 228]. Staged buccal mucosa graft requires a redo grafting in 13% of patients, after the second stage more than one third of patients have complications, mostly with some degree of graft fibrosis [235, 237]. A recent long-term study on two-stage flap repair showed a complication rate of 68% [228], another study showed a re-operation rate of 28% [211, 228].

3.5.6 Follow-up

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions and recurrent penile curvature. Up to half of complications requiring re-operation present after the first year post-operatively [238] (LE: 2b).

Obstructive flow curve is common after hypospadias repair and while most are not clinically significant, long-term follow-up is required [239-242] (LE: 2a). Urine flow is significantly lower in patients after hypospadias surgery, especially in those who had corrected chordee, but without significant association with lower urinary symptoms [243] (LE: 2a).

Objective scoring systems have been developed in order to evaluate the results of hypospadias surgery (HOSE) [244] (LE: 2b) and cosmetic appearance (HOPE-Hypospadias Objective Penile Evaluation) [245] (LE: 2a). The Pediatric Penile Perception Score (PPPS) is a reliable instrument to assess penile self-perception in children after hypospadias repair and for appraisal of the surgical result by parents and uninvolved urologists [246] (LE: 2a).

Adolescents and adults, who have undergone hypospadias repair in childhood, have a slightly higher rate of dissatisfaction with penile size, especially proximal hypospadias patients, but their sexual behaviour is not different from that of control groups [247, 248] (LE: 2a-b). Another long-term follow-up of men born with hypospadias revealed, in a controlled study, that these patients are less satisfied with penile cosmetic outcome according to all parameters of the PPS, there was a difference in penile length (9.7 vs 11.6 cm) and more patients had lower maximum urinary flow; and more prominent results were found in proximal hypospadias vs. controls [228, 249].

According to a systematic review of long-term patient satisfaction with cosmetic outcomes [250]:

- patient perception of penile size does not differ greatly from the norm;
- patients approaching puberty have a more negative perception and are more critical about the cosmetic outcomes of surgery;
- patients report high levels of perception of deformity and social embarrassment.

3.5.7 Summary of evidence and recommendations for the management of hypospadias

Summary of evidence	LE
The suggested age at surgery for primary hypospadias repair is 6 - 18 (24) months.	3
The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the new meatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance.	4
Androgen stimulation therapy results in increased penile length and glans circumference.	1B
The complication rate is about 10% in distal and 25% in proximal hypospadias one-stage repairs. Higher and variable rate (between 28 and 68%) can occur in two-stage repairs.	3
Sexual functions are usually well preserved.	2b

Recommendations	GR
At birth, differentiate isolated hypospadias from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	A
Counsel parents on functional indications for surgery, aesthetically feasible operative procedures (psychological, cosmetic indications) and possible complications.	A
In children diagnosed with proximal hypospadias and a small appearing penis, reduced glans circumference or reduced urethral plate, pre-operative hormonal androgen stimulation treatment is an option and the body of evidence to accentuate its harms and benefits is inadequate.	B
For distal hypospadias, use original and modified tubularised incised plate urethroplasty; use the onlay urethroplasty or two-stage procedures in more severe hypospadias. A treatment algorithm is presented (Figure 3). Correct significant (> 30 degrees) curvature of the penis.	B
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature.	A
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	A

3.6 Congenital penile curvature

3.6.1 Epidemiology, aetiology and pathophysiology

Congenital penile curvature presents penile bending of a normally formed penis due to corporal disproportion. The incidence at birth is 0.6% and congenital penile curvature is caused by asymmetry of the cavernous bodies but an orthotopic meatus [251] because of developmental arrest during embryogenesis [252]. On the other hand the incidence of clinically significant congenital penile curvature is much lower, because the extent of the curvature and its associated sexual dysfunction varies widely [253]. Most of the cases are ventral deviations (48%), followed by lateral (24%), dorsal (5%), and a combination of ventral and lateral (23%) [254]. Most ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies [255]. Similarly, dorsal curvature is mostly associated with exstrophy/epispadias complex.

Curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood (LE: 4). Minor penile curvature may be the result of ventral penile skin deficiency only and should be distinguished from corporal anomalies. For penile curvature associated with hypospadias or epispadias refer to the relevant chapters.

3.6.2 Diagnostic evaluation

Penile curvature is frequently not documented until later in childhood since the penis only appears abnormal when erect. Patients are usually concerned with the aesthetic and/or functional aspects of their penis [256]. Besides exact history taking to exclude any possibility of acquired penile curvature (e.g. post-traumatic) a thorough clinical examination is mandatory. In addition photo documentation of the erect penis clearly showing the curvature from different angles serves as a pre-requisite in pre-operative evaluation [257]. The exact degree of curvature is generally determined at the time of surgery using an artificial erection test.

3.6.3 Management

The treatment is surgical, starting with an artificial erection to determine the degree of curvature and to check symmetry after the repair [258]. The ultimate goal of any surgical method used to correct the curvature is to achieve corpora of similar size. Various procedures are in use ranging from rather simple de-gloving and plication procedures, to corporal rotation, use of free dermal or tunica vaginalis grafts, to complete penile disassembly techniques [259, 260]. Reviews comparing the outcome of Nesbit/modified Nesbit procedures [261] to plication procedures [262] were able to demonstrate that while there is a decreased risk of

complications and loss of sensation, it remains unclear whether plication techniques can lead to increased risk of recurrence [263]. Altogether these methods include the risk of post-operative shortening of the penis with an average loss of 2.5 cm in stretched penile length depending on the pre-operative degree of curvature and the type of repair used [264, 265].

Recently the non-corporotomy technique has been introduced with promising results enabling correction of any degree of ventral curvature with neither shortening of the penis nor the risk of post-operative erectile dysfunction [266].

3.6.4 **Summary of evidence and recommendations for the management of congenital penile curvature**

Summary of evidence	LE
Isolated congenital penile curvature is relatively uncommon.	2a
Congenital penile curvature is often associated with hypospadias.	2a
Diagnosis is usually made late in childhood.	2a
The penis only appears abnormal when erect.	1b
Congenital penile curvature can cause aesthetic as well as functional sexual problems.	1b
Congenital penile curvature is treated with surgery.	1b
The goal of surgery is to achieve corpora of similar size.	1b

Recommendations	LE	GR
Ensure that a thorough medical history is taken and a full clinical examination done to rule out associated anomalies in boys presenting with congenital curvature.	1a	A
Provide photo documentation of the erect penis from different angles as a prerequisite in the preoperative evaluation.	1b	A
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	2b	B
At the beginning as well as at the end of surgery perform artificial erection tests.	2a	A

3.7 **Varicocele in children and adolescents**

3.7.1 Epidemiology, aetiology and pathophysiology

Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under ten years of age and becomes more frequent at the beginning of puberty. It is found in 14-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are less common; they are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding [267-269].

Varicocele develops during accelerated body growth and increased blood flow to the testes, by a mechanism that is not clearly understood. Genetic factors may be present. An anatomic abnormality leading to impaired venous drainage is expressed by the considerable prevalence of the left side condition where the internal spermatic vein drains into the renal vein. Varicocele can induce apoptotic pathways because of heat stress, androgen deprivation and accumulation of toxic materials. Severe damage is found in 20% of adolescents affected, with abnormal findings in 46% of affected adolescents. Histological findings are similar in children or adolescents and in infertile men. In 70% of patients with grade II and III varicocele, left testicular volume loss was found.

Several authors reported on reversal of testicular growth after varicocelectomy in adolescents [270, 271]. An average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a recent meta-analysis [272] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [273] (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise [274]. The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [275-278] (LE: 1).

3.7.1 **Classification systems**

Varicocele is classified into 3 grades [279]:

- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);
- Grade II - palpable (palpable without the Valsalva manoeuvre);
- Grade III - visible (visible at distance).

3.7.2 **Diagnostic evaluation**

Varicocele is mostly asymptomatic, rarely causing pain. It may be noticed by the patient or parents, or discovered by the paediatrician at a routine visit. The diagnosis depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; the veins are more pronounced when the patient performs the Valsalva manoeuvre. The size of both testicles should be evaluated during palpation to detect a smaller testis.

Venous reflux into the plexus pampiniformis is diagnosed using Doppler US colour flow mapping in the supine and upright position [280]. Venous reflux detected on US only is classified as subclinical varicocele. To discriminate testicular hypoplasia, the testicular volume is measured by US examination or by orchidometer. In adolescents, a testis that is smaller by > 2 mL or 20% compared to the other testis is considered to be hypoplastic [281] (LE: 2).

Extension of Wilms tumour into the renal vein and inferior vena cava can cause a secondary varicocele. A renal US should be routinely added in pre-pubertal boys and in isolated right varicocele (LE: 4).

In order to assess testicular injury in adolescents with varicocele, supranormal FSH and LH responses to the luteinising hormone-releasing hormone (LHRH) stimulation test are considered reliable, because histopathological testicular changes have been found in these patients [276, 282].

3.7.3 **Management**

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later. Beneficial effect of pubertal screening and treatment for varicocele regarding chance of paternity has been questioned according to a corresponding questionnaire in adult patients [283] (LE: 4). The recommended indication criteria for varicocelectomy in children and adolescents are [268]:

- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- symptomatic varicocele [283].

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available [284]. Repair of a large varicocele, causing physical or psychological discomfort, may also be considered. Other varicoceles should be followed-up until a reliable sperm analysis can be performed (LE: 4).

Surgical intervention is based on ligation or occlusion of the internal spermatic veins. Ligation is performed at different levels:

- inguinal (or subinguinal) microsurgical ligation;
- suprainguinal ligation, using open or laparoscopic techniques [285-288].

The advantage of the former is the lower invasiveness of the procedure, while the advantage of the latter is a considerably lower number of veins to be ligated and safety of the incidental division of the internal spermatic at the suprainguinal level.

For surgical ligation, some form of optical magnification (microscopic or laparoscopic) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring [285, 287]. The recurrence rate is usually < 10%.

Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy development and to achieve a better testicular function according to the LHRH stimulation test [273, 285, 286, 289] (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [285, 287, 290, 291]. Intrascrotal application of isosulphan blue was recommended to visualise the lymphatic vessels [292, 293]. In suprainguinal approach, an artery sparing varicocelectomy may not offer any advantage in regards to catch-up growth and is associated with a higher incidence of recurrent varicocele [294, 295].

Angiographic occlusion of the internal spermatic veins also meets the requirements of lymphatic sparing repair. It is based on retrograde or antegrade sclerotisation of the internal spermatic veins [296, 297]. However, although this method is less invasive and may not require general anaesthesia, it is associated with radiation burden, which is less controllable in the antegrade technique [268, 296, 297] (LE: 2).

3.7.4 **Summary of evidence and recommendations for the management of varicocele**

Summary of evidence	LE
Varicocele becomes more frequent at the beginning of puberty and is found in 14-20% of adolescents. Fertility problems are expected in up to 20% of adolescents with a varicocele.	
Pubertal patients with a left grade II and III varicocele have the left testis smaller in up to 70%; in late adolescence the contralateral right testis also becomes smaller.	1b
After adolescent varicocelectomy, left testis catch-up growth and improvement in sperm parameters has been demonstrated.	1a
There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later.	1b
Division of testicular lymphatics leads to hydrocele in up to 40% and to testicular hypertrophy.	1b

Recommendations	LE	GR
Examine varicocele in the standing position and classify into three grades.	4	A
Use scrotal ultrasound to detect venous reflux without Valsalva manoeuvre in the supine and upright position and to discriminate testicular hypoplasia.		
In pre-pubertal boys and in isolated right varicocele perform standard renal ultrasound to exclude a retroperitoneal mass.		
Perform surgery for: <ul style="list-style-type: none"> varicocele associated with a small testis (size difference of > 2 mL or 20%); additional testicular condition affecting fertility; pathological sperm quality (in older adolescents); bilateral palpable varicocele; symptomatic varicocele. 	2	B
Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	2	B
Use lymphatic-sparing varicocelectomy to prevent hydrocele formation and testicular hypertrophy.	2	A

3.8 **Urinary tract infections in children**3.8.1 **Epidemiology, aetiology and pathophysiology**

Urinary tract infections represent the most common bacterial infection in children [298-300]. In neonates, the symptoms differ in many aspects from those in infants and children. The prevalence is higher; there is a male predominance; infections not caused by *Escherichia coli* are more frequent; and there is a higher risk of urosepsis [301-304].

The incidence varies depending on age and sex. One meta-analysis showed in the first three months of life UTIs were present in 7.5% of girls, 2.4% (CI: 1.4-3.5) of circumcised boys, and 20.1% (CI: 16.8-23.4) of uncircumcised boys, who presented with fever [302]. In the first year of life, UTIs are more common in boys (3.7%) than girls (2%). Later, the incidence of UTIs changes to ~3% in pre-pubertal girls and 1% in pre-pubertal boys [302-305].

E. coli is found in ~75% of UTIs and is more frequent in community-acquired than nosocomial infections. In the latter, *Klebsiella pneumoniae*, *Enterobacter spp.*, *Enterococcus spp.*, *Pseudomonas spp.* and *Candida spp.* are more frequent than in community-acquired UTIs. Neonatal UTI is frequently complicated by bacteraemia. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteraemia [306], however, it is less frequent in community-acquired than in nosocomial UTI [306, 307].

3.8.2 **Classification systems**

There are five widely used classification systems according to; the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.

3.8.2.1 **Classification according to site**

Lower urinary tract (cystitis) is an inflammatory condition of the urinary bladder mucosa with general signs and symptoms including infection, dysuria, frequency, urgency, malodorous urine, enuresis, haematuria, and suprapubic pain.

Upper urinary tract (pyelonephritis) is a diffuse pyogenic infection of the renal pelvis and parenchyma. The onset of pyelonephritis is generally abrupt. Clinical signs and symptoms include fever (> 38°C), chills, costovertebral angle or flank pain, and tenderness. Older children may report cystitis symptoms

along with fever/flank pain. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea.

3.8.2.2 *Classification according to episode*

The first UTI may be a sign of anatomical anomalies that may predispose to complications of UTI and potential renal damage [308]. Anatomical evaluation is recommended (see below). Recurrent infection can be divided into unresolved and persistent infection.

In unresolved infection, initial therapy is inadequate for elimination of bacterial growth in the urinary tract (inadequate therapy, inadequate antimicrobial urinary concentration [poor renal concentration/gastrointestinal malabsorption], and infection involving multiple organisms with differing antimicrobial susceptibilities).

Persistent infection is caused by re-emergence of bacteria from a site within the urinary tract coming from a nidus for persistent infection that cannot be eradicated (e.g. infected stones, non-functioning or poorly functioning kidneys/renal segments, ureteral stumps after nephrectomy, necrotic papillae in papillary necrosis, urachal cyst, urethral diverticulum, periurethral gland, vesicointestinal, rectourethral or vesicovaginal fistulas). The same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment.

In re-infection, each episode can be caused by a variety of new infecting organisms, in contrast to bacterial persistence in which the same infecting organism is always isolated. However, the most common general pathogenic species is *E. coli*, which occurs in many different serotypes. Therefore, recurrent *E. coli* UTI does not equate to infection with the same organism.

3.8.2.3 *Classification according to severity*

In simple UTI, children may have only mild pyrexia; are able to take fluids and oral medication; are only slightly or not dehydrated; and have a good expected level of compliance. When a low level of compliance is expected, such children should be managed as those with severe UTI. In severe UTI, infection is related to the presence of fever of > 39°C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

3.8.2.4 *Classification according to symptoms*

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that are incapable of activating a symptomatic response (no leukocyturia, no symptoms). Asymptomatic UTI includes leukocyturia but no other symptoms.

A symptomatic UTI, includes irritative voiding symptoms, suprapubic pain (cystitis), fever and malaise (pyelonephritis). Cystitis may represent early recognition of an infection destined to become pyelonephritis, or bacterial growth controlled by a balance of virulence and host response.

3.8.2.5 *Classification according to complicating factors*

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal upper and lower urinary tract, normal renal function and competent immune system. This category includes mostly isolated or recurrent bacterial cystitis and is usually associated with a narrow spectrum of infecting pathogens that are easily eradicated by a short course of oral antimicrobial agents. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract [309].

All neonates, most patients with clinical evidence of pyelonephritis, and all children with known mechanical or functional obstructions of the urinary tract, are considered to have complicated UTI. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent of their location. Functional obstruction often results from lower urinary tract dysfunction (LUTD) of either neurogenic or non-neurogenic origin and dilating vesicoureteral reflux (VUR). Patients with complicated UTI require hospitalisation and parenteral antibiotics. Prompt anatomical evaluation of the urinary tract is critical to exclude the presence of significant abnormalities [310]. If mechanical or functional abnormalities are present, adequate drainage of the infected urinary tract is necessary.

3.8.3 **Diagnostic evaluation**

3.8.3.1 *Medical history*

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or post-natal US screening); prior operation; family history; and whether there is constipation or presence of lower urinary tract symptoms (LUTS).

3.8.3.2 *Clinical signs and symptoms*

Neonates with pyelonephritis or urosepsis can present with non-specific symptoms (failure to thrive, jaundice,

hyperexcitability and without fever). Urinary tract infection is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic [311-313]. Septic shock is unusual, even with very high fever. Signs of a UTI may be vague and unspecific in small children, but later on, when they are more than two years old, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain can be detected.

3.8.3.3 *Physical examination*

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), and temperature.

3.8.3.4 *Urine sampling, analysis and culture*

Urine sampling has to be performed before any antimicrobial agent is administered. The technique for obtaining urine for urinalysis as well as culture affects the rate of contamination, which influences interpretation of the results. Especially in early infancy it can be challenging and depends on the mode of urine sampling [314].

3.8.3.4.1 *Urine sampling*

Urine must be collected under defined conditions and investigated as soon as possible to confirm or exclude UTI, especially in children with fever. In neonates, infants and non-toilet-trained children, there are four main methods with varying contamination rates and invasiveness to obtain urine:

(1) Plastic bag attached to the cleaned genitalia: This technique is most often used in daily practice. It is helpful when the culture results are negative. Also, if the dipstick is negative for both leukocyte esterase and nitrite, or microscopic analysis is negative for both pyuria and bacteriuria, UTI can be excluded without the need for confirmatory culture [315]. However, if the genitalia are not cleaned and culture is delayed, a high incidence of false-positive results (85-99%) can be found [316, 317].

(2) Clean-catch urine collection: The infant is placed in the lap of a parent or member of the nursing staff, who holds a sterile foil bowl underneath the infant's genitalia. The infant is offered oral fluids and urine collection is awaited [318]. This is time consuming and requires proper instruction of the parents. There seems to be a good correlation between the results of urine culture obtained by this method and suprapubic aspiration (SPA), with a false-positive rate of 5% and false-negative rate of 12% [318, 319]; however the contamination rate is higher compared to SPA [320].

(3) Bladder catheterisation: In female infants and also in neonates, this technique may be an alternative to SPA, however with a higher contamination rate [321]. In a prospective study using bladder catheterisation in febrile children aged < 36 months, contamination was defined by multiple pathogens, non-pathogens, or colony counts < 10,000 cfu/mL. True UTI was found in 10% of children and 14% of the cultures were contaminated. Univariate analysis of potential predictors identified age less than six months, difficult catheterisation, and uncircumcised boys. In children less than six months and uncircumcised boys a new, sterile catheter with each repeated attempt at catheterisation may lead to less contamination [322] otherwise SPA should be the method of choice.

(4) Suprapubic bladder aspiration: This is the most sensitive method to obtain an uncontaminated urine sample in this age group [322-324]. Using US to assess bladder filling, simplifies SPA and improves the diagnostic yield of obtaining a urine specimen from 60% to 97% [323, 324]. Complications are rare and have been reported in only 0.22% of cases, ranging from transient haematuria to bowel perforation [325]. However, bladder puncture causes more pain than catheterisation in infants less than two months old [326].

In older, toilet-trained, children who can void on command, after carefully retracting the foreskin and cleaning the glans penis in boys and spreading the labia and cleaning the peri-urethral area in girls, the use of clean catch, especially midstream urine, could be an acceptable technique for obtaining urine. After cleaning the urethral meatus and perineum with gauze and liquid soap twice, the risk of contamination was reduced from 23.9% (41/171) to 7.8% (14/171) in a randomised trial [327].

If the clinical situation necessitates, and for differential diagnosis of sepsis, it is most appropriate to obtain an adequate urine sample by catheterisation or SPA [319]. In infants, a bag can only be used if the dipstick is negative, otherwise the urine should be obtained through catheterisation or SPA. This is also recommended in children, who are severely ill and a UTI needs to be excluded or confirmed. Blood sampling is dependent on the clinical situation.

3.8.3.4.2 Urinalysis

There are three methods that are commonly used for urinalysis:

(1) Dipsticks: These are appealing because they provide rapid results, do not require microscopy, and are ready to use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers, and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria takes approximately four hours in the bladder [319, 328]. However, nitrite is not a very sensitive marker for infants, who empty their bladder frequently, and not all urinary pathogens reduce nitrate to nitrite. The test is helpful when the result is positive, because it is highly specific (i.e. there are few false-positive results) [319, 329].

Table 1: Sensitivity and specificity of component of urinalysis, alone and in combination [319]*

Test	Sensitivity (Range), %	Specificity (Range), %
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy, white blood cells	73 (32-100)	81 (45-98)
Microscopy, bacteria	81 (16-99)	83 (11-100)
Leucocyte esterase test, nitrite test or microscopy positive	99.8 (99-100)	70 (60-92)

*Reproduced with permission from Pediatrics 2011 Sep;128(3):595-610, Copyright© 2011 by the AAP [319].

(2) Microscopy: This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of five white blood cells (WBCs) per high-power field (25 WBC/ μ L) [325]. In uncentrifuged urine, > 10 WBC/ μ L has been demonstrated to be sensitive for UTI [330] and this could perform well in clinical situations [331]. However, this is rarely done in an outpatient setting.

(3) Flow imaging analysis technology: This is being used increasingly to classify particles in uncentrifuged urine specimens [332]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [319].

3.8.3.4.3 Urine culture

After negative results for dipstick, microscopic or automated urinalysis, urine culture is generally not necessary, especially if there is an alternative source of fever. If the dipstick result is positive, confirmation by urine culture is strongly recommended.

It is unclear what represents a significant UTI. In severe UTI, $> 10^5$ cfu/mL can be expected. However, the count can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs [304]. The classical definition of $> 10^5$ cfu/mL of voided urine is still used to define a significant UTI [333, 334]. The American Academy of Pediatric Guidelines on Urinary Tract Infection suggest that the diagnosis should be on the basis of the presence of both pyuria and at least 10^5 cfu/mL. However, some studies have shown that, in voided specimens, $< 10^4$ organisms may indicate a significant UTI [335, 336]. If urine is obtained by catheterisation, $10^3 - 10^5$ cfu/mL is considered to be positive, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination.

Table 2: Criteria for UTI in children (adapted from the EAU Guidelines on Urological Infections [337])

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	$> 10^3 - 10^5$ cfu/mL	$> 10^4$ cfu/mL with symptoms $> 10^5$ cfu/mL without symptoms

Pyuria without bacteriuria (sterile pyuria) may be due to incomplete antibiotic treatment, urolithiasis, or foreign bodies in the urinary tract, and infections caused by *Mycobacterium tuberculosis* or *Chlamydia trachomatis*.

3.8.3.5 Imaging

3.8.3.5.1 Ultrasound

Renal and bladder US within 24 hours is advised in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. Abnormal results are found in 15% of cases, and 1-2% have abnormalities that

require prompt action (e.g. additional evaluation, referral, or surgery) [319]. In other studies, renal US revealed abnormalities in up to 37% of cases, whereas voiding cystourethrography (VCUG) showed VUR in 27% of cases [307]. Dilating VUR is missed by US in around one third of cases [338]. Post-void residual (PVR) urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI. Elevated post-void residual urine volume predicts recurrence of UTIs in toilet-trained children [339].

3.8.3.5.2 Radionuclide scanning

Changes in dimercaptosuccinic acid (DMSA) clearance during acute UTI indicate pyelonephritis or parenchymal damage, correlated well with the presence of dilating reflux and the risk of further pyelonephritis episodes, breakthrough infections [340] and future renal scarring. In the acute phase of a febrile UTI (up to four to six weeks), DMSA-scan can demonstrate pyelonephritis by perfusion defects. Renal scars can be detected after three to six months [338, 341]. These findings are different in neonates. After the first symptomatic, community-acquired UTI, the majority of renal units with VUR grade III or higher had normal early DMSA scanning [342]. See also Chapter 3.13 on VUR.

3.8.3.5.3 Voiding cystourethrography

The gold standard to exclude or confirm VUR is VCUG. Due to the risk of renal scarring, VCUG is recommended after the first episode of febrile UTI in boys and girls depending on sex, age and clinical presentation (see Figure 4 and Table 4) (see also Chapter 3.13). The timing of VCUG does not influence the presence or severity of VUR [343, 344]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [345]. Another option is doing DMSA first, followed by VCUG if there is renal cortical uptake deficiency after UTI (see Chapter 3.13).

3.8.3.6 Bladder and bowel dysfunction

Bladder and bowel dysfunction (BBD) are risk factors for which each child with UTI should be screened upon presentation. Normalisation of micturition disorders or bladder over-activity is important to lower the rate of UTI recurrence. If there are signs of BBD at infection-free intervals, further diagnosis and effective treatment are strongly recommended [346-349]. Treatment of constipation leads to a decrease in UTI recurrence [350-352]. Therefore, exclusion of BBD is strongly recommended in any child with febrile and/or recurrent UTI, and it should be treated if there is evidence of BBD.

3.8.4 Management

3.8.4.1 Administration route

The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g. urinary obstruction). As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged less than two months, parenteral antibiotic therapy is recommended. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudohypoaldosteronism can occur in these cases [353, 354].

Parental combination treatment with ampicillin and an aminoglycoside (e.g. tobramycin or gentamicin) or respectively a third-generation cephalosporin achieves excellent therapeutic results (high efficacy of aminoglycosides, respectively cephalosporins against common uropathogens; enterococcus gap is closed with ampicillin). Compared to the division in two doses, a daily single dose of aminoglycosides is safe and effective [310, 355, 356].

The choice of agent is also based on local antimicrobial sensitivity patterns, and should later be adjusted according to sensitivity testing of the isolated uropathogen [319]. Not all available antibiotics are approved by the national health authorities, especially in infancy. In uncomplicated nephritis, both oral and parenteral treatment can be considered, because both are equally effective in children without urinary tract abnormalities. Some studies have demonstrated that once daily parenteral administration of gentamicin or ceftriaxone in a day treatment centre is safe, effective and cost-effective in children with UTI [355, 357, 358].

3.8.4.2 Duration of therapy

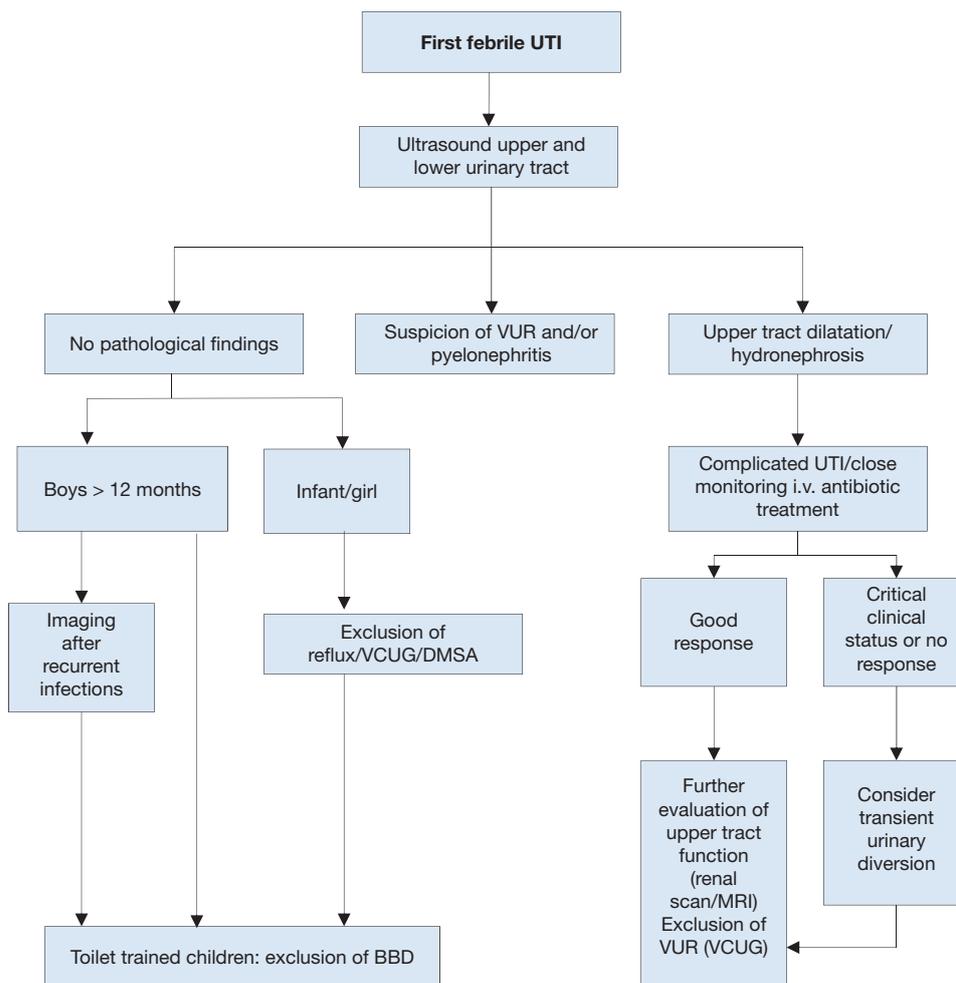
Prompt adequate treatment of UTI can prevent the spread of infection and renal scarring. Outcomes of short courses (one to three days) are inferior to those of seven to fourteen-day courses [319]. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [306, 310]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [359]. Some recent studies using exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) have demonstrated that this is equivalent to the usual two to four days intravenous therapy followed by oral treatment [356, 360-362]. Similar data have been shown for amoxicillin-clavulanate [363], however, these antibiotics are associated with increasing rates of resistance. If ambulatory therapy is chosen, adequate

surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, a close ambulant contact to the family is advised [364].

In complicated UTI, uropathogens other than *E. coli*, such as *Proteus mirabilis*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, *enterococci* and *staphylococci*, are more often the causative pathogens [310]. Parenteral treatment with broad-spectrum antibiotics is preferred. A temporary urinary diversion (suprapubic-cystostomy or percutaneous nephrostomy) might be required in case of failure of conservative treatment in obstructive uropathy. Acute focal bacterial nephritis (lobar nephronia) is a localised bacterial infection of the kidney that presents as an inflammatory mass without abscess formation. This may represent a relatively early stage of renal abscess. For the majority of children, the pathogenesis is related to ascending infection due to pre-existing uropathy, especially vesicorenal reflux or urinary obstruction (megaureter).

Prolonged intravenous antibiotic treatment is sufficient in most cases [365], and intravenous and oral therapy tailored to the pathogen identified in culture is recommended [366].

Figure 4: Algorithm for disease management of first febrile UTI



BBD = Bladder Bowel Dysfunction; DMSA = technetium⁹⁹-labelled dimercaptosuccinic acid; MRI = magnetic resonance imaging; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.

3.8.4.3 Antimicrobial agents

There is a great difference in the prevalence of antibiotic resistance of uropathogenic *E. coli* in different countries, with an alarmingly high resistance in Iran and Vietnam [367]. There are upcoming reports of UTIs caused by extended spectrum β -lactamase-producing enterobacteriaceae (ESBL) in children. In one study from Turkey, 49% of the children less than one year of age and 38% of those more than one year of age had ESBL-producing bacteria that were resistant to trimethoprim/sulfamethoxazole in 83%, to nitrofurantoin in 18%, to quinolones in 47%, and to aminoglycosides in 40% [368]. Fortunately, the outcome appears to be the same as for children with non-ESBL-producing bacteria, despite the fact that initial intravenous empirical antibiotic therapy was inappropriate in one study [369].

Table 3: Frequently used antibacterial substances for the therapy of urinary tract infections in infants and children*

Chemotherapeutics	Daily dosage	Application	Comments
Parenteral cephalosporins			
Group 3a, e.g. cefotaxime	100-200 mg/kg (Adolesc.: 3-6 g)	i.v. in 2-3 D	
Group 3b, e.g. ceftazidime	100-150 mg/kg (Adolesc.: 2-6 g)	i.v. in 2-3 D	
Ceftriaxone	75 mg/kg	i.v. in 1 D	
Oral cephalosporins			
Group 3, e.g. ceftibuten	9 mg/kg (Adolesc.: 0.4 g)	p.o. in 1-2 D	
Group 3, e.g. cefixime	8-12 mg/kg (Adolesc.: 0.4 g)	p.o. in 1-2 D	
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kg (Adolesc.: 0.4 g)	p.o. in 2 D	
Group 2, e.g. cefuroximaxetil	20-30 mg/kg (Adolesc.: 0.5-1 g)	p.o. in 3 D	
Group 1, e.g. cefaclor	50 -100 mg/kg (Adolesc.: 1.5-4 g)	p.o. in 2-3 D	
Trimethoprim or Trimethoprim/sulfamethoxazole	5-6 mg/kg 5-6 mg/kg (TMP-Anteil) (Adolesc.: 320 mg)	p.o. in 2 D p.o. in 2 D	
Ampicillin	100-200 mg/kg (Adolesc.: 3-6 g)	i.v. in 3 D	Ampicillin and Amoxicillin are not eligible for calculated therapy
Amoxicillin	50-100 mg/kg (Adolesc.: 1.5-6 g)	i.v. in 3-4 D p.o. in 2-3 D ¹	
Amoxicillin/clavulanic acid (parenteral)	60-100 mg/kg (Adolesc.: 3.6-6.6 g)	p.o. in 2-3 D i.v. in 3 D	
Amoxicillin/clavulanic acid (oral)	45-60 mg/kg (Amoxicillinfraction) (Adolesc.: 1500 + 375 mg)	i.v. in 3 D p.o. in 3 D	
Piperacillin	300 mg/kg	p.o. in 3 D	
Tobramycin	5 mg/kg (Adolesc.: 3-5 mg/ kg, max. 0.4 g)	i.v. in 3-4 D	
Gentamicin	5 mg/kg (Adolesc.: 3-5 mg/ kg, max. 0.4g)	i.v. in 1 D	Drug monitoring
Ciprofloxacin	Children and adolesc. (1-17 years of age): 20-30 mg/kg (max. D: 400 mg) (parenterally)	i.v. in 3 D	Approved in most European countries as second- or third line medication for complicated UTIs, "reserve-antibiotic"!
	Children and adolesc. (1-17 years of age): 20-40 mg/kg (max. D 750 mg) (orally)	p.o. in 2 D	
Nitrofurantoin	3-5 mg	p.o. in 2 D	Contraindicated in the case of renal insufficiency

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Dosage for adolescents in paracentesis, if differing. 1 Infants 2 D, children 1-12 ys. 3 D.

i.v. = intravenous; p.o. = by mouth.

Table 4: Recommendations for calculated antibacterial therapy of pyelonephritis dependent on age and severity of the infection*

Diagnosis	Proposal	Application	Duration of therapy	LE
Pyelonephritis during the first 0-6 months of life	Ceftazidime + Ampicillin ¹ or Aminoglycoside + Ampicillin ¹	3-7 D parenterally, for at least 2 D after defervescence, then oral therapy ² In newborns: parenteral therapy for 7-14 D, then oral therapy ²	10 (-14) D Newborns 14-21 D	4
Uncomplicated pyelonephritis after 6 months of age	Cephalosporin group 3 ²	Orally (initially parenterally, if necessary)	(7-)10 D	1
Complicated pyelonephritis/urosepsis (all ages)	Ceftazidime + Ampicillin ¹ or Aminoglycoside + Ampicillin ¹	7 D parenterally, then oral therapy ²	10-14 D	4

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1 after receipt of microbiological findings (pathogen, resistance) adaptation of therapy.

2 i.v.: e.g. cefotaxime; orally: e.g. cefpodoxime proxetil, ceftibuten, cefixime.

Table 5: Frequently used antibacterial agents used for the treatment of cystitis and cystourethritis (Dosages for children up to twelve years of age)*

Chemotherapeutics	Daily dosage	Application
Oral cephalosporins		
Group 1, e.g. cefaclor	50 (-100) mg/kgbw	p.o. in 2-3 D
Group 1, e.g. cefalexin	50 mg/kgbw	p.o. in 3-4 D
Group 2, e.g. cefuroximaxetil	20-30 mg/kgbw	p.o. in 2 D
Group 2, e.g. cefpodoxime proxetil	8-10 mg/kgbw	p.o. in 2 D
Group 3, e.g. ceftibuten	9 mg/kgbw	p.o. in 1 D
Trimethoprim	5-6 mg/kgbw	p.o. in 2 D
Trimethoprim/sulfamethoxazole	5-6 mg/kgbw (TMP-fraction)	p.o. in 3 D
Amoxicillin/clavulanic acid	37.5-75 mg/kgbw (Amoxicillin-fraction)	p.o. in 3 D
Nitrofurantoin	3-5 mg/kgbw	p.o. in 2 D

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3.8.4.4 Chemoprophylaxis

Long-term antibacterial prophylaxis should be considered in cases of high susceptibility to UTI and risk of acquired renal damage. Some recently published prospective, randomised studies do not support the efficacy of antibacterial prophylaxis [371-374]. However, two recently published prospective randomised trails as well as one meta-analysis demonstrated a significant risk reduction of developing another UTI by using continuous antibiotic prophylaxis [360, 375, 376] (see also Chapter 3.13 on VUR).

Cranberry juice as well as probiotics may also prevent recurrence of UTI as demonstrated by RCTs [377-379]. A cochrane review could not rule out some benefit of using probiotics [380].

Table 6: Drugs for antibacterial prophylaxis*

Substance	Prophylactic dosage (mg/kg bw/d)	Limitations in neonates and infants
Trimethoprim**	1	Until six weeks of age
Trimethoprim Sulfamethoxazole	1-2 10-15	Not recommended under two months of age
Nitrofurantoin**	1	Until three months of age
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns
Ceftibuten	2	***
Cefuroximaxetil	5	***

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** Substances of first choice are nitrofurantoin and trimethoprim. In exceptional cases, oral cephalosporin can be used.

*** In Germany, ceftibuten is not approved for infants < 3 months old.

3.8.4.5 Monitoring of UTI

With successful treatment, urine usually becomes sterile after 24 hours, and leukocyturia normally disappears within three to four days. Normalisation of body temperature can be expected within 24-48 hours after the start of therapy in 90% of cases. In patients with prolonged fever and failing recovery, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Immediate US examination is recommended in these cases.

Procalcitonin (among other laboratory inflammatory parameters such as C-reactive protein and leukocyte count) can be used as reliable serum marker for early prediction of renal parenchymal inflammation with first febrile UTI [381]. In patients with febrile UTI, serum electrolytes and blood cell counts should be obtained.

3.8.5 Summary of evidence and recommendations for the management of UTI in children

Summary of evidence	LE
Urinary tract infection represents the most common bacterial infection in children less than 2 years of age. The incidence varies depending on age and sex.	1b
Classifications are made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.	2b
The number of colony forming units (cfu) in the urine culture can vary and is related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs.	2b
The classical definition of > 10 ⁵ cfu/mL in voided urine is still used to define a significant UTI.	3
Changes in DMSA clearance during acute UTI indicate pyelonephritis or parenchymal damage. If it is positive, reflux may be present.	2a

Recommendations	LE	GR
Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	3	A
Exclude bladder- and bowel dysfunction in any child with febrile and/or recurrent UTI.	3	A
Do not delay diagnosis and treatment of bladder-bowel-dysfunction.	2a	A
Collect an uncontaminated urine sample in an infant through suprapubic bladder aspiration. Bladder catheterisation is an alternative (traumatic especially in boys).	2a	B
Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results. Clean catch urine is an acceptable technique for toilet-trained children.	2a	B
Urinalysis by dipstick yields rapid results, but it should be used with caution. Microscopic investigation is the standard method of assessing pyuria after centrifugation. Using flow imaging analysis, the numbers of white blood cells (WBCs), squamous epithelial cells and red cells correlate well with manual methods.	2a	B
The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; complicated pyelonephritis.	2a	B
Treat UTIs with four to seven day courses of oral or parenteral therapy. Do not use of short courses (one to three days) since outcomes are inferior.	1b	B
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms (LUTS).	1b	B
Treat complicated UTI, with broad-spectrum antibiotics (parenteral).	1b	B
In infants with febrile UTI, use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract.	3	B
In all infants, exclude vesicoureteral reflux (VUR) after the first episode of febrile UTI, using voiding cystourethrography (VCUG) or a dimercaptosuccinic acid (DMSA) scan first (in case of a positive DMSA-scan, follow-up with VCUG). In boys more than one year of age, exclude VUR after the second febrile UTI.	2a	B

3.9 Day-time lower urinary tract conditions

3.9.1 *Epidemiology, aetiology and pathophysiology*

Day-time LUT conditions are conditions that present with LUTS, including urgency, urge incontinence, weak stream, hesitancy, frequency and UTIs without overt uropathy or neuropathy. Following the newest terminology document by the International Children's Continence Society (ICCS), 'day-time LUT conditions' is the new term used to group together functional incontinence problems in children [382]. After any possible underlying uropathy or neuropathy has been excluded, a problem of incontinence in children is grouped into the category of 'day-time LUT conditions'. Night-time wetting is known as 'enuresis'.

Due to the relationship between the bladder and bowel, concomitant bladder and bowel disturbances have been labelled as bladder bowel dysfunction (BBD). The use of the terms dysfunctional elimination syndrome (DES) or voiding dysfunction are discouraged. Bladder bowel dysfunction is an umbrella term that can be subcategorised into LUT dysfunction and bowel dysfunction.

Although exact data are unavailable, it is clear that the incidence of day-time LUT conditions is increasing. Awareness and better access to specialised health care can be one of the reasons for this observation. Reported prevalence ranges widely from 2% to 20% [383-387]. This wide variation might reflect the variation in definitions used. In recent studies, bowel dysfunction is observed in > 50 % of children suffering LUT dysfunction [388, 389].

3.9.2 *Classification systems*

Various functional disorders of the detrusor-sphincter complex may occur during the sophisticated early development of normal mechanisms of micturition control. Lower urinary tract conditions are therefore thought to be the expression of incomplete or delayed maturation of the bladder sphincter complex. Normal day-time control of bladder function matures between two and three years of age, while night-time control is normally achieved between three and seven years of age [383]. There are two main groups of LUTD, namely, filling-phase dysfunctions and voiding-phase dysfunctions. As compared to the general population, in children LUT conditions present with higher prevalence of comorbidities such as Attention Deficit and Hyperactivity Disorder (ADHD) [390, 391].

3.9.2.1 *Filling-phase dysfunctions*

In filling-phase dysfunctions, the detrusor can be overactive, as in overactive bladder (OAB), or underactive, as in underactive bladder (UAB). Some children habitually postpone micturition leading to voiding postponement.

3.9.2.2 *Voiding-phase (emptying) dysfunctions*

In voiding-phase (emptying) dysfunctions, sphincter and pelvic floor interference during detrusor contraction is the main dysfunction. The general term for this condition is dysfunctional voiding. Different degrees of dysfunction are described, depending on the strength of interference with the sphincter and pelvic floor. Weak interference results in staccato voiding, while stronger interference results in interrupted voiding and straining, due to an inability to relax during voiding.

3.9.3 **Diagnostic evaluation**

A non-invasive screening, consisting of history-taking, clinical examination, uroflow, US and voiding diary, is essential to reach a diagnosis [391]. In the paediatric age group, where the history is taken from both the parents and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the parents and should be specifically requested, using the questionnaire as a checklist. A voiding diary is mandatory to determine the child's voiding frequency and voided volumes as well as the child's drinking habits. History-taking should also include assessment of bowel function. Some dysfunctional voiding scores have recently been developed and validated [392, 393]. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [394, 395].

Upon clinical examination, genital inspection and observation of the lumbosacral spine and the lower extremities are necessary to exclude obvious uropathy and neuropathy. Uroflow with post-void residual evaluates the emptying ability, while an UUT US screens for secondary anatomical changes. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss.

In the case of resistance to initial treatment, or in the case of former failed treatment, re-evaluation is warranted and further video-urodynamic (VUD) studies may be considered. Sometimes, there are minor, underlying, urological or neurological problems, which can only be suspected using VUD. In these cases, structured psychological interviews to assess social stress should be added [396] (LE: 1b).

In the case of anatomical problems, such as posterior urethral valve problems, syringocoeles, congenital obstructive posterior urethral membrane (COPUM) or Moormann's ring, it may be necessary to perform further cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

3.9.4 **Management**

Treatment of LUTD consists of LUT rehabilitation, mostly referred to as urotherapy, meaning non-surgical, non-pharmacological, treatment of LUT function. It is a very broad therapy field, incorporating many treatments used by urotherapists and other healthcare professionals [397]. In case of comorbidity due to bowel problems it is advised to treat the bowel first, since bowel problems may sustain any bladder problems [394]. Urotherapy can be divided into standard therapy and specific interventions. It is strongly advised not to use terms such as "standard therapy" or "maintenance therapy" without defining the design of these treatments.

3.9.4.1 *Standard therapy*

In case of combined bladder- and bowel dysfunction it is advised to treat the bowel dysfunction first [389] as LUTS may disappear after successful management of bowel dysfunction. Standard urotherapy is defined as non-surgical, non-pharmacological, treatment for LUTD. It can include the following components:

- Information and demystification, which includes explanation about normal LUT function and how a particular child deviates from normal function.
- Instruction about what to do about the problem, i.e. regular voiding habits, sound voiding posture, avoiding holding manoeuvres, etc.
- Lifestyle advice, regarding fluid intake, prevention of constipation, etc.
- Registration of symptoms and voiding habits using bladder diaries or frequency-volume charts.
- Support and encouragement via regular follow-up by the caregiver.

A success rate of 80% has been described for urotherapy programmes, independent of the components of the programme. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled. A recently published multicentre controlled trial of cognitive treatment, placebo, oxybutynin, bladder and pelvic floor training did not report better results with oxybutynin and pelvic floor training compared to standard therapy [396] (LE: 1b).

3.9.4.2 Specific interventions

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neurostimulation. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only a few RCTs were published [350, 397-402]. Two RCTs on underactive bladder without neurophatic disease have recently been published. Transcutaneous interferential electrical stimulation and animated biofeedback with pelvic floor exercise have been shown to be effective [403, 404]. In some cases, pharmacotherapy may be added. Antispasmodics and anticholinergics have been shown to be effective, although the level of evidence was low. Some studies on orthosympathomimetics have been published with a low level of evidence [405].

A few RCTs have been published, one on tolterodine showed safety but not efficacy [406], while another on propiverine showed both safety and efficacy [407] (LE: 1). The difference in results is probably due to study design. Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended because of the large number of studies reporting a positive effect on OAB symptoms. Although α -blocking agents are used occasionally, an RCT showed no benefit [408]. Botulinum toxin injection seems promising, but can only be used off-label [409]. Other new treatment modalities such as sacral nerve stimulation are described in case series only and there is no evidence for their usefulness. These new treatment modalities can only be recommended for standard therapy resistant cases [410]. A recent ICCS standardisation document on treatment of day-time incontinence gives an excellent overview of treatment modalities [390].

3.9.5 Summary of evidence and recommendations for the management of day-time lower urinary tract conditions

Summary of evidence	LE
The term; 'bladder bowel dysfunction' is to be used rather than 'dysfunctional elimination syndrome and voiding dysfunction'.	4
Day-time LUTS has a high prevalence (2% to 20%).	2

Recommendations	LE	GR
Use a stepwise approach, starting with the least invasive treatment in managing day-time lower urinary tract dysfunction (LUTD) in children.	4	B
Initially offer urotherapy involving: non-invasive training and re-education, and non-invasive neurostimulation.	2	B
If present, treat bladder bowel dysfunction bowel dysfunction first, before treating the lower urinary tract condition.	2	B
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second line therapy.	1	C
Re-evaluate in case of therapy resistance; this may consist of videourodynamics and magnetic resonance imaging of lumbosacral spine, guiding to off-label treatment (e.g. some of the non-licensed drugs in children, botulinum toxin injection and sacral nerve stimulation). Such treatment should only be offered in highly experienced centres.	3	C

3.10 Monosymptomatic enuresis

3.10.1 Epidemiology, aetiology and pathophysiology

Enuresis is synonymous to intermittent nocturnal incontinence. It is a frequent symptom in children. With a prevalence of 5-10% at seven years of age, it is one of the most prevalent conditions in childhood. With a spontaneous yearly resolution rate of 15%, it is considered relatively benign [411, 412]. Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry. The term "secondary nocturnal enuresis" is used when a child or adult begins wetting again after having stayed dry.

However, seven out of 100 children wetting the bed at age seven will take this condition into adulthood. As it is a stressful condition, which puts a high psychological burden on children resulting in low self-esteem, treatment is advised from the age of six to seven years onwards. Treatment is unnecessary in younger children in whom spontaneous cure is likely. The child's mental status, family expectations, social issues and cultural background need to be considered before treatment can be started.

Genetically, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 [413].

Three factors play an important pathophysiological role:

- high night-time urine output;
- night-time low bladder capacity or increased detrusor activity;
- arousal disorder.

Due to an imbalance between night-time urine output and night-time bladder capacity, the bladder can become easily full at night and the child will either wake up to empty the bladder or will void during sleep if there is a lack of arousal from sleep [411-413]. Recently, attention has been given to the chronobiology of micturition in which the existence of a circadian clock in kidney, brain and bladder [414] (LE: 1).

3.10.2 **Classification systems**

Enuresis is the condition describing the symptom of incontinence during night. Any wetting during sleep above the age of five years is enuresis. However, most importantly, there is a single symptom only. Children with other LUTS and enuresis are said to have non-monosymptomatic enuresis [411]. Thorough history-taking, excluding any other day-time symptoms, is mandatory before diagnosing monosymptomatic enuresis. Any associated urinary tract symptoms make the condition a 'day-time LUT condition' [413].

The condition is described as 'primary' when the symptom has always existed and the patient has not been dry for a period longer than six months. The condition is described as 'secondary', when there has been a symptom-free interval of six months.

3.10.3 **Diagnostic evaluation**

The diagnosis is obtained by history-taking. In a patient with monosymptomatic enuresis, no further investigations are needed. A voiding diary, which records day-time bladder function and night-time urine output, will help to guide the treatment. An estimate of night-time urine production can be obtained by weighing diapers (nappies) in the morning and adding the volume of the morning void. Measuring the day-time bladder capacity gives an estimate of bladder capacity compared to normal values for age [415].

Ultrasound of the urinary tract is not recommended but, when available, it can be used to exclude underlying pathology. In most children, bedwetting is a familial problem, with most affected children found to have a history of bedwetting within the family. A urinary dipstick may help differentiate between true enuresis resulting from polyuria due to diabetes insipidus.

3.10.4 **Management**

Before using alarm treatment or medication, simple therapeutic interventions should be considered.

3.10.4.1 *Supportive treatment measures*

Explaining the condition to the child and the parents helps to demystify the problem. Eating and drinking habits should be reviewed, stressing normal fluid intake during the day and reducing fluid intake in the hours before sleep. Keeping a chart depicting wet and dry nights has been shown to be successful.

Counselling, provision of information, positive reinforcement, and increasing (and supporting) motivation of the child should be introduced first. A recent Cochrane review shows that simple behavioural interventions can be effective. However, other proven therapies like enuresis alarm and tricyclic antidepressants are more effective [416] (LE:1a).

3.10.4.2 *Alarm treatment*

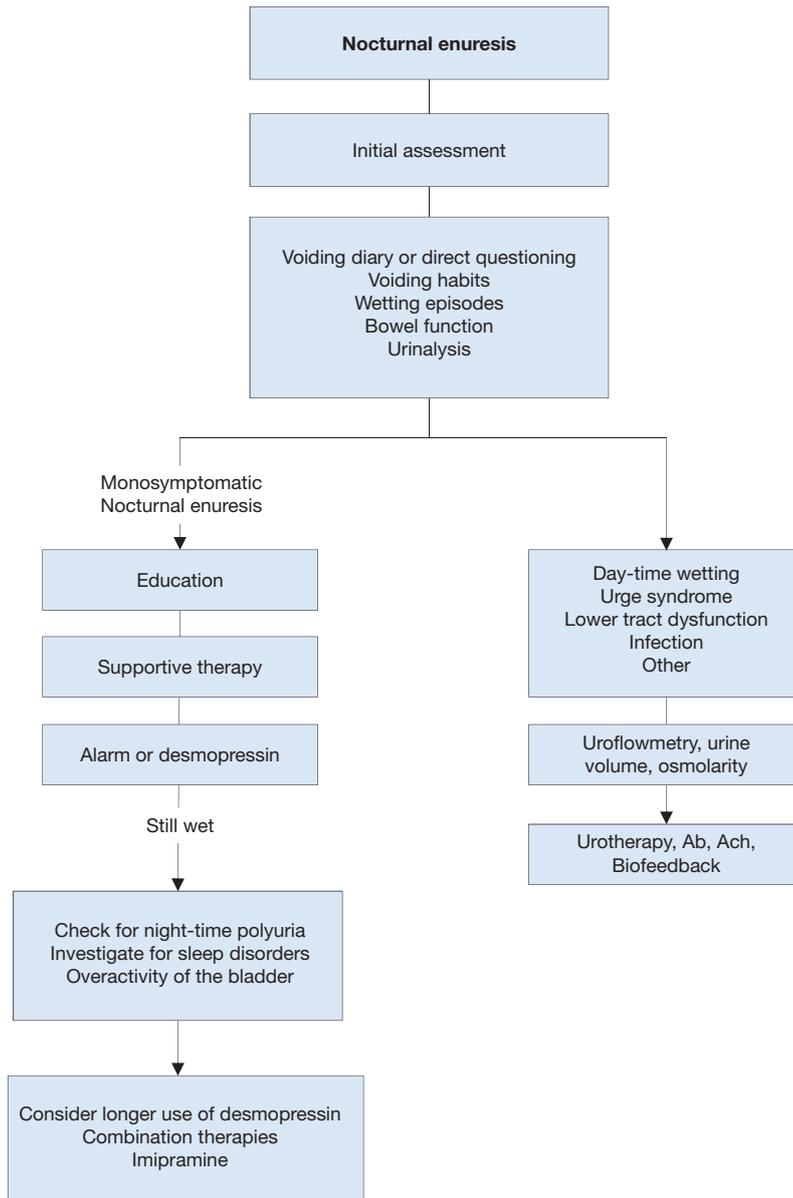
Alarm treatment is the best form for arousal disorder (LE: 1). Initial success rates of 80% are realistic, with low relapse rates, especially when night-time diuresis is not too high and bladder capacity is not too low [417].

3.10.4.3 *Medication*

In the case of high night-time diuresis, success rates of 70% can be obtained with desmopressin (DDAVP), either as tablets (200-400 µg), or as sublingual DDAVP oral lyophilisate (120-240 µg). A nasal spray is no longer recommended due to the increased risk of overdose [418, 419] (LE: 1). Relapse rates are high after DDAVP discontinuation [415] however recently, structured withdrawal has shown lower relapse rates [420] (LE: 1).

In the case of small bladder capacity, treatment with antispasmodics or anticholinergics is possible [415]. However, when these medications are necessary, the condition is no longer considered to be monosymptomatic. Imipramine, which has been popular for treatment of the enuresis, achieves only a moderate response rate of 50% and has a high relapse rate. Furthermore, cardiotoxicity and death from overdose are described, its use should therefore be discouraged as the first line therapy [421] (LE: 1). Figure 5 presents stepwise assessment and management options for nocturnal enuresis.

Figure 5: Assessment and management of nocturnal enuresis



Ab = antibody; Ach = acetylcholine.

3.10.5 Summary of evidence and recommendations for the management of monosymptomatic enuresis

Summary of evidence	LE
Chronobiology of micturition in which the existence of a circadian clock has been proven in kidney, brain and bladder and disturbances in this chronobiology play a major role in the pathophysiology of enuresis.	1

Recommendations	LE	GR
Do not treat children less than 5 years of age in whom spontaneous cure is likely.	2	A
Use voiding diaries or questionnaires to exclude day-time symptoms.	2	A
Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	2	B
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important. When used alone they have limited success.	1	A

Offer alarm treatment for arousal disorder with low relapse rates. There may be family compliance problems.	1	A
Offer desmopressin for the treatment of night-time diuresis. The response rate is high around 70%; relapse rates are high.	1	A
Ensure structured withdrawal of desmopressin to improve relapse rates.	1	A
Ensure that the parents are well informed about the problem. The advantages and disadvantages of each of the two treatment modalities should be explained. The choice of the treatment modality can be made during parental counselling.	4	B

3.11 Management of neurogenic bladder

3.11.1 *Epidemiology, aetiology and pathophysiology*

Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of LUTD, which may lead to incontinence, UTIs, VUR, and renal scarring. Surgery may be required to establish adequate bladder storage and drainage. If not managed properly, NDSD can potentially cause renal failure, requiring dialysis or transplantation. The main goals of treatment are prevention of urinary tract deterioration and achievement of continence at an appropriate age.

The management of neurogenic bladder sphincter dysfunction in children has undergone major changes over the years. Although nappies (diapers), permanent catheters, external appliances, Crede's manoeuvre and various forms of urinary diversion have been acceptable treatment methods, these are now reserved for only a small number of resistant patients. The introduction of clean intermittent catheterisation (IC) has revolutionised the management of children with neurogenic bladder. Not only has it made conservative management a very successful treatment option, but it has also made surgical creation of continent reservoirs a very effective treatment alternative, with a good outcome for quality of life and kidney protection [422-424].

Neurogenic bladder in children with myelodysplasia presents with various patterns of DSD with a wide range of severity. About 15% of neonates with myelodysplasia have no signs of neuro-urological dysfunction at birth. However, there is a high chance of progressive changes in the dynamics of neurological lesions with time. Even babies with normal neuro-urological function at birth have a one in three risk of developing either detrusor sphincter dyssynergia or denervation by the time they reach puberty. At birth, the majority of patients have normal UUTs, but nearly 60% of them develop upper tract deterioration due to infections, bladder changes and reflux [425-428].

The most common presentation at birth is myelodysplasia. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions may include spina bifida occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental. Traumatic and neoplastic spinal lesions of the cord are less frequent in children. Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion. Scar tissue surrounding the cord at the site of meningocele closure can tether the cord during growth. In occult myelodysplasia, the lesions are not overt and often occur with no obvious signs of neurological lesion. In nearly 90% of patients, however, a cutaneous abnormality overlies the lower spine, and this condition can easily be detected by simple inspection of the lower back [429].

Total or partial sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae. This anomaly can be part of the caudal regression syndrome, and must be considered in any child presenting with anorectal malformation (ARM). Patients with cerebral palsy may also present with varying degrees of voiding dysfunction, usually in the form of uninhibited bladder contractions (often due to spasticity of the pelvic floor and sphincter complex) and wetting. Bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion.

3.11.2 *Classification systems*

The purpose of any classification system is to facilitate the understanding and management of the underlying pathology. There are various systems of classification of neurogenic bladder.

Most systems of classification were formulated primarily to describe those types of dysfunction secondary to neurological disease or injury. Such systems are based on the localisation of the neurological lesion and the findings of the neuro-urological examination. These classifications have been of more value in adults, in whom neurogenic lesions are usually due to trauma and are more readily identifiable.

In children, the spinal level and extent of congenital lesion are poorly correlated with the clinical outcome. Urodynamic and functional classifications have therefore been more practical for defining the extent of the pathology and planning treatment in children.

The bladder and sphincter are two units working in harmony to make a single functional unit. The initial approach should be to evaluate the state of each unit and define the pattern of bladder dysfunction.

According to the nature of the neurological deficit, the bladder and sphincter may be in either an overactive or inactive state:

- the bladder may be overactive with increased contractions, and low capacity and compliance, or inactive with no effective contractions;
- the outlet (urethra and sphincter) may be independently overactive causing functional obstruction, or paralysed with no resistance to urinary flow;
- these conditions may present in different combinations.

This is mainly a classification based on urodynamic findings. The understanding of the pathophysiology of disorders is essential to plan a rational treatment plan for each individual patient. In meningocele, most patients will present with hyper-reflexive detrusor and dyssynergic sphincter, which is a dangerous combination as pressure is built up and the upper tract is threatened.

3.11.3 **Diagnostic evaluation**

3.11.3.1 *Urodynamic studies*

Since the treatment plan mainly depends upon a good understanding of the underlying problem in the LUT, a well-performed urodynamic study is mandatory in the evaluation of each child with neurogenic bladder. As the bony level often does not correspond with the neurological defect present, and as the effect of the lesion on bladder function cannot be entirely determined by radiographic studies or physical examination, the information gained from a urodynamic study is crucial. A urodynamic study also provides the clinician with information about the response of the vesicourethral unit to therapy, as demonstrated by improvement or deterioration in follow-up.

It is important to determine several urodynamic parameters, including:

- the bladder capacity;
- the intravesical filling pressure;
- the intravesical pressure at the moment of urethral leakage;
- the presence or absence of reflex detrusor activity;
- the competence of the internal and external sphincteric mechanisms;
- the degree of coordination of the detrusor and sphincteric mechanisms;
- the voiding pattern;
- the post-voiding residual urine volume.

3.11.3.1.1 Method of urodynamic study

There is very little comparative data evaluating the complexity and invasiveness of urodynamic testing for neurogenic bladders in children.

3.11.3.1.2 Uroflowmetry

As uroflowmetry is the least invasive of all urodynamic tests, it can be used as an initial screening tool. It provides an objective way of assessing the efficiency of voiding, and, together with an ultrasonographic examination, the residual urine volume can also be determined. Unlike in children with non-neurogenic voiding dysfunction, uroflowmetry will rarely be used as a single investigational tool in children with neurogenic bladders, as it does not provide information on bladder storage, yet it may be very practical to monitor emptying in the follow-up. The main limitation of a urodynamic study is the need for the child to be old enough to follow instructions and void on request.

Recording of pelvic floor or abdominal skeletal muscle activity by electromyography (EMG) during uroflowmetry can be used to evaluate coordination between detrusor and the sphincter. As it is a non-invasive test, combined uroflowmetry and EMG may be very useful in evaluating sphincter activity during voiding [430-433] (LE: 3; GR: C).

3.11.3.2 *Cystometry*

Although moderately invasive and dependent on a co-operative child, cystometry in children provides valuable information regarding detrusor contractility and compliance. The amount of information obtained from each study is related to the degree of interest and care given to the test.

It is important to be aware of the alterations in filling and emptying detrusor pressures as the infusion rates change during cystometry. Slow fill cystometry (filling rate < 10 mL/min) is recommended by the ICCS for use in children [434]. However, it has been suggested that the infusion rate should be set according to the child's predicted capacity, based on age and divided by 10 or 20 [412].

Several clinical studies using conventional artificial fill cystometry to evaluate neurogenic bladder in children have reported that conventional cystometry provides useful information for diagnosis and follow-up

of children with neurogenic bladder [435-440]. All of the studies were retrospective clinical series and lacked comparison with natural fill cystometry, so that the grade of recommendation for an artificial cystometry in children with neurogenic bladder is not high (LE: 4). Additionally, there is evidence suggesting that natural bladder behaviour is altered during regular artificial filling cystometry [441-444].

Conventional cystometry in infants is useful for predicting future deterioration. Urodynamic parameters, such as low capacity, compliance and high leak-point pressures, are poor prognostic factors for future deterioration. Resolution of reflux is less likely to happen in such bladders [435, 439, 441] (LE: 4). Although there are only a few studies on natural fill cystometry in children with neurogenic bladder, the results suggest that natural fill cystometry detects new findings compared with diagnoses delivered by conventional cystometry [442] (LE: 3). However, the comparison between natural- and artificial fill cystometry has not been performed against a gold standard, making it difficult to conclude which study is a true reflection of natural bladder behaviour. Findings in the non-neurogenic adult population have questioned the reliability of natural fill cystometry, as it has shown a high incidence of bladder over-activity in totally normal asymptomatic volunteers [445]. The main disadvantage of natural fill cystometry is that it is labour-intensive and time-consuming. Moreover, because of the transurethral catheter used during this study, false-positive findings caused by the catheter are possible. Especially in children, the recording of events is difficult and there is an increased risk of artefacts, which makes interpretation of the huge amount of data even more difficult. Natural fill cystometry remains a new technique in the paediatric population. More data need to be gathered in a standard way before it can be widely accepted [433].

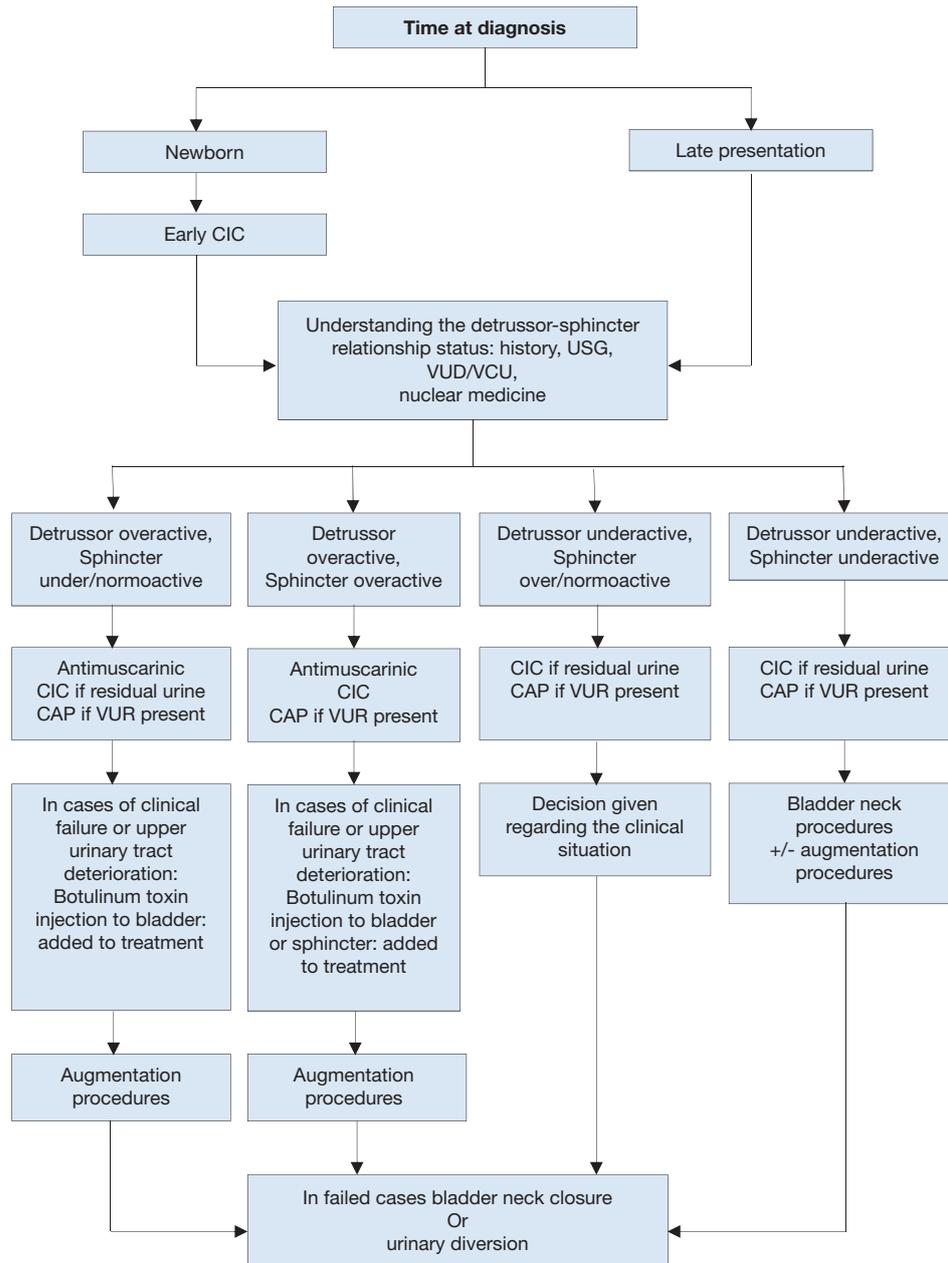
The timing of the first urodynamic study is not clear. However, repeat studies should be done in a child with neurogenic bladder who are not responsive to the initial treatment or in whom a change in treatment or an intervention is planned.

3.11.4 *Management*

The medical care of children with myelodysplasia with a neurogenic bladder requires constant observation and adaptation to new problems. In the first years of life, the kidneys are highly susceptible to back-pressure and infection. During this period, the emphasis is on documenting the pattern of NDSD and assessing the potential for functional obstruction and VUR. The early study and treatment of patients is essential for decreasing renal impairment, reducing the need for surgery and improving the continence options [446].

A simple algorithm can be used for management of these patients (Figure 6).

Figure 6: Algorithm for the management of children with myelodysplasia with a neurogenic bladder



CAP = continuous antibiotic prophylaxis; CIC = clean intermittent catheterisation; US = ultrasound; VCUG = voiding cystourethrography; VUD = videourodynamic; VUR = vesicoureteric reflux.

3.11.4.1 Investigations

An abdominal US obtained as soon as possible after birth will detect hydronephrosis or other upper genitourinary tract pathology. Following US, a VCUG, preferably a VUD study should be obtained to evaluate the LUT. Measurement of residual urine during both US and cystography should also be done. These studies provide a baseline for the appearance of the upper and lower urinary tracts, can facilitate the diagnosis of hydronephrosis or VUR, and can help identify children at risk for upper genitourinary tract deterioration and impairment of renal function.

A urodynamic evaluation can be done after some weeks, and needs to be repeated at regular intervals, in combination with evaluation of the upper tract [447-449] (LE: 3).

3.11.4.2 Early management with intermittent catheterisation

Overwhelming experience gained over the years with early management of neurogenic bladder in infants has led to a consensus that children do not have upper tract deterioration when managed early with IC and anticholinergic medication. Intermittent catheterisation should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction [349, 447, 450-457] (LE: 2). In babies without any

clear sign of outlet obstruction, may be delayed but these babies should be monitored for UTIs and upper tract changes.

The early initiation of IC in the newborn period makes it easier for parents to master the procedure and for children to accept it, as they grow older [458, 459].

Early management results in fewer upper tract changes, but also better bladder protection and lower incontinence rates. It has been suggested that increased bladder pressures due to detrusor sphincter dyssynergia causes secondary changes of the bladder wall. These fibroproliferative changes in the bladder wall may cause further loss of elasticity and compliance, resulting in a small non-compliant bladder with progressively elevated pressures.

Early institution of IC and anticholinergic drugs may prevent this in some patients [424, 457, 460] (LE: 3). The retrospective evaluation of patients has also shown that significantly fewer augmentations were required in patients with an early start of IC [451, 456] (LE: 4).

3.11.4.3 *Medical therapy*

At present, oxybutynin, tolterodine, trospium and propiverine are the most frequently used drugs, with oxybutynin being the most studied. The dosage for oxybutynin is 0.1-0.3 mg/kg given three times daily. In case of side effects intravesical administration may be considered.

Two different forms of tolterodine have been investigated in children with neurogenic bladder. The extended release formulation of tolterodine has been found to be as efficient as the instant release form, with the advantages of being single dose and less expensive. Although the clinical outcome is encouraging, the level of evidence is low for anticholinergic medication because there are no controlled studies [460-467] (LE: 3). The use of medication to facilitate emptying in children with neurogenic bladder has not been well studied in the literature. A few studies investigating the use of α -adrenergic blockade in children with neurogenic bladder have reported a good response rate, but the studies lacked controls, and long-term follow-up is warranted [468] (LE: 4).

Botulinum toxin injections: In neurogenic bladders that are refractory to anticholinergics, injection of botulinum toxin into the detrusor muscle is a novel treatment alternative. Initial promising results in adults has resulted in its use in children. It has been shown that this treatment has beneficial effects on clinical and urodynamic variables. Complete continence was achieved in 65-87% of patients; in most studies mean maximum detrusor pressure was reduced to at least 40 cmH₂O and bladder compliance was increased to at least 20 cmH₂O/mL. However, findings are limited by the lack of controlled trials and studies involving small patient numbers [409, 469-473]. Botulinum toxin seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond [473-478].

The most commonly used dose of botulinum toxin is 10 U/kg with a maximum dose of 200 U. No dose study has been performed in children and there is no evidence regarding the optimal dose. Currently, it is unclear how many times this treatment can be repeated, although repetitive treatment has been found to be safe in adults [409, 479-481].

Injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative (LE: 3). Urethral sphincter botulinum-A toxin injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [482, 483].

3.11.4.4 *Management of bowel incontinence*

Children with neurogenic bladder have disturbances of bowel function as well as urinary function. Bowel incontinence in these children is frequently unpredictable. It is related to the turnover rate of faecal material in the anal area after evacuation, the degree of intactness of sacral cord sensation and motor function, and reflex reactivity of the external anal sphincter [484].

Bowel incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. A regular and efficient bowel emptying regimen is often necessary to maintain faecal continence, and may have to be started at a very young age. With antegrade or retrograde enemas, most children will have decreased constipation problems and may attain some degree of faecal continence [485-489] (LE: 3).

Biofeedback training programmes to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management programme in achieving faecal continence [490]. Electrostimulation of the bowel may also offer a variable improvement in some patients [491] (LE: 3).

3.11.4.5 *Urinary tract infection*

Urinary tract infections are common in children with neurogenic bladders. In the absence of reflux, UTIs should be treated symptomatically. Although bacteriuria is seen in more than half of children on CIC, patients who

are asymptomatic do not need treatment [492-494] (LE: 3). Patients with VUR should usually be placed on prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage [495, 496].

3.11.4.6 *Sexuality*

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. However, patients with myelodysplasia do have sexual encounters. Studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. It is therefore important to counsel patients about sexual development in early adolescence.

3.11.4.7 *Bladder augmentation*

Children with a good response to anticholinergic treatment and an overactive sphincter may be continent between catheterisations. Bladder pressure and development of the UUT will determine whether additional treatment is necessary or not. Therapy-resistant overactivity of the detrusor, or small capacity and poor compliance, will usually need to be treated by bladder augmentation. A simple bladder augmentation using intestine may be carried out if there is any bladder tissue, a competent sphincter and/or bladder neck, and a urethra that can be catheterised.

Stomach is rarely used as an augmenting patch because of the associated complications [497]. Ileal or colonic patches are frequently used for augmenting the bladder, with either equally useful. Despite some advantages (e.g. avoiding mucus, decreased malignancy rate and fewer complications), alternative urothelium preserving techniques, such as autoaugmentation and seromuscular cystoplasty, have not proven to be as successful as standard augmentation with intestine [498, 499].

3.11.4.8 *Bladder outlet procedures*

Children with detrusor overactivity and underactive sphincters will have better protection of their upper tracts, although they will be severely incontinent. Initial treatment is IC (as it might reduce the degree of incontinence and offers much better control over UTIs) with anticholinergic drugs. At a later age, the outlet resistance will be increased in order to render them continent. No available medical treatment has been validated to increase bladder outlet resistance. α -adrenergic receptor stimulation of the bladder neck has not been very effective [500-505].

When conservative measures fail, surgical procedures need to be considered for maintaining continence. Although a simple augmentation is sufficient for most low-capacity, high-pressure bladders, augmentation with additional bladder outlet procedures is required when both the bladder and outlet are deficient. Bladder outlet procedures include bladder neck reconstruction or other forms of urethral reconstruction.

Various procedures can be used on the bladder neck to increase resistance, but all of them may complicate transurethral catheterisation. Augmentation with surgical closure of the bladder neck may be required primarily, or as a secondary procedure in certain rare clinical situations. In this situation, a continent stoma will be required. However, most surgeons prefer to leave the bladder neck and urethra patent as a safety precaution. Application of artificial urinary sphincters (AUS) in children is another option, which gives the patient the opportunity to void spontaneously. The largest paediatric series in the literature reports a continence rate over 85% [506]. However, the decision to implant an AUS in a child raises the issue of mechanical failure (> 30%), revision of the functioning sphincter (> 15%) and surgical complication (15%). Although, advancement of newer devices decreased these numbers [506].

3.11.4.9 *Continent stoma*

Augmentation with an additional continent stoma is utilised primarily after failure of previous bladder outlet surgery. It is also advisable when an inability to catheterise transurethrally is likely. An abdominal wall continent stoma may be particularly beneficial to wheelchair-bound spina bifida patients, who often have difficulty with urethral catheterisation or are dependent on others to catheterise the bladder. For continence with augmentation and an abdominal wall stoma, an adequate bladder outlet mechanism is essential.

3.11.4.10 *Total bladder replacement*

Total bladder replacement in anticipation of normal voiding in children is very rare, as there are infrequent indications for a total cystectomy, with preservation of the bladder outlet and a competent urethral sphincter. This type of bladder replacement is much more common in adult urological reconstruction. Any type of major bladder and bladder outlet construction should be performed in centres with sufficient experience in the surgical technique, and with experienced healthcare personnel to carry out post-operative follow-up [507-509].

3.11.5 Follow-up

Neurogenic bladder patients require lifelong supervision, and the monitoring of renal and bladder function is extremely important. Periodic investigation of upper tract changes, renal function and bladder status is mandatory. Repeat urodynamic tests are therefore needed more frequently (every year) in younger children and less frequently in older children. From the urological viewpoint, a repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure. In the case of any apparent changes in the UUT and LUT, or changes in neurological symptoms, a more detailed examination including urodynamics and spinal MRI is indicated.

Renal failure can progress slowly or occur with startling speed in these children. Patients who have undergone reconstructive procedures using intestine should be regularly followed up for complications such as infection, stone formation, reservoir rupture, metabolic changes, and malignancy [507].

The risk of malignancy in enteric augmentations has been reported to be higher than expected, and the risk increases with length of follow-up. Malignancy occurs in 0.6-2.8% of patients during median follow-up of 13-21 years [510-515]. In a study including 153 patients with a median follow-up time of 28 years [512], malignancy was found in 4.5%. The malignancy seemed to be associated with coexisting carcinogenic stimuli or with the inherent risk present with bladder exstrophy. Although there are poor data on follow-up schemes; after a reasonable follow-up time (e.g. ten years), an annual diagnostic work-up including cystoscopy should be considered.

3.11.6 Summary of evidence and recommendations for the management of neurogenic bladder

Summary of evidence	LE
Neurogenic detrusor-sphincter dysfunction may result in different forms of LUTD and ultimately result in incontinence, UTIs, VUR, and renal scarring.	2a
In children, the most common cause of NDSD is myelodysplasia (a group of developmental anomalies that result from defects in neural tube closure).	2
Bladder sphincter dysfunction correlates poorly with the type and level of the spinal cord lesion. Therefore, urodynamic and functional classifications are more practical in defining the extent of the pathology and in guiding treatment planning.	2a
Children with neurogenic bladder can have disturbances of bowel function as well as urinary function which require monitoring and, if needed, management.	2a
The main goals of treatment are prevention of urinary tract deterioration and achievement of continence at an appropriate age.	2a
Injection of botulinum toxin into the detrusor muscle in children who are refractory to anticholinergics, has been shown to have beneficial effects on clinical and urodynamic variables.	2a

Recommendations	LE	GR
In all babies, start intermittent catheterisation soon after birth, except for babies without any clear sign of outlet obstruction. If intermittent catheterisation is delayed, closely monitor babies for urinary tract infections and upper tract changes.	2	B
Use anticholinergic drugs as initial treatment in children with overactive bladders. Clinical improvement is common but usually insufficient.	2	B
Use injection of botulinum toxin into the detrusor muscle as an alternative in children who are refractory to anticholinergics.	2	B
Use a bladder augmentation procedure, using a segment of intestine, in case of therapy-resistant overactivity of the detrusor, or small capacity and poor compliance causing upper tract damage and incontinence.	2	B
Use augmentation with additional bladder outlet procedures when both the bladder and outlet are deficient. Simple augmentation will suffice in most low-capacity, high-pressure bladders.	3	B
Augment with an additional continent stoma after bladder outlet surgery and in patients with urethral catheterisation limitations.	3	B
Follow-up of neurogenic bladder patients will be life-long. Follow-up includes monitoring of renal and bladder function as well as ensuring that sexuality and fertility issues receive particular care as the child gets older and moves into adulthood.	3	B

3.12 Dilatation of the upper urinary tract (UPJ and UVJ obstruction)

3.12.1 Epidemiology, aetiology and pathophysiology

Dilatation of the UUT remains a significant clinical challenge in deciding which patient will benefit from

treatment. Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter with subsequent dilatation of the collecting system and the potential to damage the kidney. It is the most common pathological cause of neonatal hydronephrosis [516]. It has an overall incidence of 1:1,500 and a ratio of males to females of 2:1 in newborns.

Ureterovesical junction (UVJ) obstruction is an obstructive condition of the distal ureter as it enters the bladder, commonly called a primary obstructive megaureter. Megaureters are the second most likely cause of neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side [517].

It can be very difficult to define 'obstruction' as there is no clear division between 'obstructed' and 'non-obstructed' urinary tracts. Currently, the most popular definition is that an obstruction represents any restriction to urinary outflow that, if left untreated, will cause progressive renal deterioration [518].

3.12.2 **Diagnostic evaluation**

The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [519]. The challenge in the management of dilated UUT is to decide which child should be observed, which child should be managed medically, and which child requires surgical intervention. Despite the wide range of diagnostic tests, there is no single test that can accurately distinguish obstructive from non-obstructive cases (see Figure 7).

3.12.2.1 *Antenatal ultrasound*

Usually between the 16th and 18th weeks of pregnancy, the kidneys are visualised routinely, when almost all amniotic fluid consists of urine. The most sensitive time for foetal urinary tract evaluation is the 28th week.

If dilatation is detected, US should focus on:

- laterality, severity of dilatation, and echogenicity of the kidneys;
- hydronephrosis or hydro-ureteronephrosis;
- bladder volume and bladder emptying;
- sex of the child;
- amniotic fluid volume [520].

3.12.2.2 *Postnatal ultrasound*

Since transitory neonatal dehydration lasts about 48 hours after birth, imaging should be performed following this period of postnatal oliguria. However, in severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended [521]. Ultrasound should assess the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine.

3.12.2.3 *Voiding cystourethrogram*

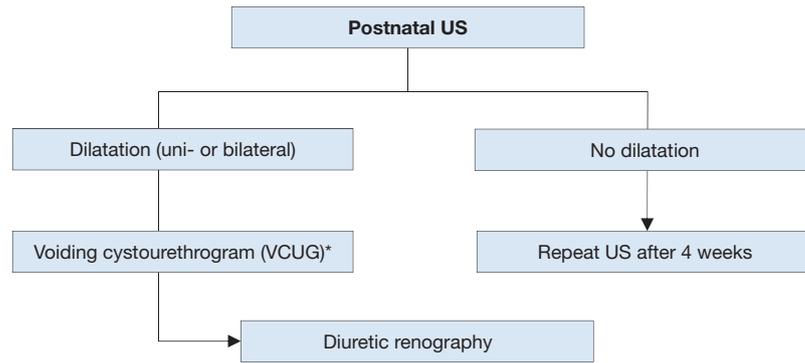
In newborns with identified UUT dilatation, the primary or important associated factors that must be detected include:

- vesicoureteral reflux (found in up to 25% of affected children) [522];
- urethral valves;
- ureteroceles;
- diverticula;
- neurogenic bladder.

Conventional VCUG is the method of choice for primary diagnostic procedures [523].

3.12.2.4 *Diuretic renography*

Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of problems with urine transport. Technetium-99m (99mTc) mercaptoacetyltriglycine (MAG3) is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) after the fourth and sixth weeks of life [524]. Oral fluid intake is encouraged prior to the examination. At fifteen minutes before the injection of the radionuclide, it is mandatory to administer normal saline intravenous infusion at a rate of 15 mL/kg over 30 minutes, with a subsequent maintenance rate of 4 mL/kg/h throughout the entire time of the investigation [525]. The recommended dose of furosemide is 1 mg/kg for infants during the first year of life, while 0.5 mg/kg should be given to children aged one to sixteen years, up to a maximum dose of 40 mg.

Figure 7: Diagnostic algorithm for dilatation of the upper urinary tract

* A diagnostic work-up including VCUG must be discussed with the parents, as it is possible that, even if reflux is detected, it may have absolutely no clinical impact. However, it should be borne in mind that reflux has been detected in up to 25% of cases of prenatally detected and postnatally confirmed hydronephrosis [522].
US = ultrasound.

3.12.3 Management

3.12.3.1 Prenatal management

Counselling the parents of an affected child is one of the most important aspects of care. The prognosis is hopeful for a hydronephrotic kidney, even if it is severely affected, as it may still be capable of meaningful renal function, unlike a severely hypoplastic and dysplastic kidney.

It is important to be able to tell the parents exactly when they will have a definitive diagnosis for their child and what this diagnosis will mean. In some cases, however, it will be immediately obvious that the child is severely affected; there will be evidence of massive bilateral dilatation, bilateral hypoplastic dysplasia, progressive bilateral dilatation with oligohydramnios, and pulmonary hypoplasia.

Intrauterine intervention is rarely indicated and should only be performed in well-experienced centres [526].

3.12.3.1.1 Antibiotic prophylaxis for antenatal hydronephrosis (ANH)

The benefits and harms of continuous antibiotic prophylaxis (CAP) vs. observation in patients with antenatal hydronephrosis are controversial. Currently, only two RCTs have been published, one of which is a pilot trial [527] and the other publication is only available as a congress abstract [528]. Both publications present incomplete data and outcomes.

The EAU Paediatric Guidelines Panel conducted a systematic review (SR) assessing the literature from 1980 onwards [4]. The key findings are summarised below:

Due to the heterogeneity of the published literature it was not possible to draw strong conclusions as to whether CAP is superior to observation alone in children diagnosed with ANH. In the first RCT, a prospective longitudinal study [527], female gender, uncircumcised males, lack of CAP, high-grade hydronephrosis, hydroureteronephrosis and VUR were found to be the independent predictors for the development of UTI. The second RCT included in the SR, was published as an abstract only, presented limited data [528]. This trial seemed to focus mainly on patients with ANH and VUR and did not report any beneficial effect of CAP on UTI rates, but details on the study population were limited.

Key findings of the SR are that CAP may or may not be superior to observation in children with antenatal hydronephrosis in terms of decreasing UTI. Due to the low data quality it was also not possible to establish whether boys or girls are at a greater risk of developing a UTI, or ascertain the presence or absence of VUR impacts UTI rates. A correlation between VUR-grade and UTI could not be established either. However, non-circumcised infants, children diagnosed with high-grade hydronephrosis and hydroureteronephrosis were shown to be at higher risk of developing a UTI.

The SR also tried to identify the most effective antibiotic regimen and present data on adverse effects but due to heterogeneity, the available data could not be statistically compared. The most commonly used antibiotic in infants with antenatal hydronephrosis is trimethoprim, but only one study reported side effects [527].

In conclusion, based on the currently available evidence, the benefits and harms of CAP in children with antenatal hydronephrosis remain unproven. Uncircumcised infants and infants with hydroureteronephrosis

and high-grade hydronephrosis are more likely to develop a UTI. Continuous antibiotic prophylaxis should be reserved for this sub-group of children who are proven to be at high risk.

3.12.3.2 UPJ obstruction

It is most important that management decisions are made on the basis of serial investigations that have used the same technique and have been performed by the same institution under standardised circumstances. Symptomatic obstruction (recurrent flank pain, UTI) requires surgical correction using a pyeloplasty, according to the standardised open technique of Hynes and Anderson [529]. In experienced hands, laparoscopic or retro-peritoneoscopic techniques and robot-assisted techniques have the same success rates as standard open procedures. In asymptomatic cases, conservative follow-up is the treatment of choice.

Indications for surgical intervention comprise impaired split renal function (< 40%), a decrease of split renal function of > 10% in subsequent studies, poor drainage function after the administration of furosemide, increased anteroposterior diameter on US, and grade III and IV dilatation as defined by the Society for Fetal Urology [530].

Well-established benefits of conventional laparoscopy over open surgery are the decreased length of hospital stay, better cosmesis, less post-operative pain and early recovery [531, 532]. A recent meta-analysis in children has shown that laparoscopic pyeloplasty (LP) was associated with decreased length of hospital stay and complication rates but prolonged operative time when compared to open pyeloplasty (OP). Additionally, both LP and OP had equal success rates [533]. Robotic-assisted laparoscopic pyeloplasty (RALP) has all the same advantages as LP plus better maneuverability, improved vision, ease in suturing and increased ergonomics but higher costs [534, 535]. There does not seem to be any clear benefit of minimal invasive procedures in a very young child but current data is insufficient to defer a cut-off age.

3.12.3.3 Megaureter

The treatment options of secondary megaureters are reviewed in Chapter 3.13.3.

3.12.3.3.1 Non-operative management

If a functional study reveals and confirms adequate ureteral drainage, conservative management is the best option. Initially, low-dose prophylactic antibiotics within the first year of life are recommended for the prevention of UTIs, although there are no existing prospective randomised trials evaluating the benefit of this regimen [536]. With spontaneous remission rates of up to 85% in primary megaureter cases, surgical management is no longer recommended, except for megaureters with recurrent UTIs, deterioration of split renal function and significant obstruction [537].

3.12.3.3.2 Surgical management

In general, surgery is indicated for symptomatic children and if there is a drop in function in conservative follow-up and hydroureteronephrosis is increasing [538]. Data suggest that children with a ureteric diameter of > 10-15 mm are more likely to require intervention [539].

The initial approach to the ureter can be either intravesical, extravesical or combined. Straightening the ureter is necessary without devascularisation. Ureteral tapering should enhance urinary flow into the bladder. The ureter must be tapered to achieve a diameter for an anti-reflux repair. Several tailoring techniques exist, such as ureteral imbrication or excisional tapering [540]. Some institutions perform endoscopic stenting, but there is still no long-term data and no prospective randomised trials to confirm their outcome.

3.12.4 Conclusion

The use of routine perinatal sonography has resulted in increased detection of hydronephrosis caused by UPJ or UVJ obstruction. Meticulous and repeat postnatal evaluation is mandatory to try to identify obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are quite standardised and have a good clinical outcome.

3.12.5 **Summary of evidence and recommendations for the management of UPJ-, UVJ-obstruction**

Summary of evidence	LE
Nowadays, most hydronephrotic kidneys have already been diagnosed prenatally during a maternal US investigation.	2
Ureteropelvic junction obstruction is the leading cause of hydronephrotic kidneys (40%).	1
In children diagnosed with antenatal hydronephrosis, a systematic review could not establish any benefits or harms related to continuous antibiotic prophylaxis.	1b
In children diagnosed with antenatal hydronephrosis, non-circumcised infants (LE: 1a), children diagnosed with high-grade hydronephrosis (LE: 2) and hydroureteronephrosis (LE: 1b) were shown to be at higher risk of developing UTI.	2

Recommendations	LE	GR
Include serial ultrasound (US) and subsequent diuretic renogram and sometimes voiding cystourethrography (VCUG) in postnatal investigations.	2	B
Offer continuous antibiotic prophylaxis to the sub-group of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection (uncircumcised infants (LE: 1a), children diagnosed with hydroureteronephrosis (LE: 2) and high-grade hydronephrosis (LE: 2)).	2	A
Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	2	B
Offer surgical intervention in case of an impaired split renal function due to obstruction or a decrease of split renal function in subsequent studies and increased anteroposterior diameter on the US, and grade IV dilatation as defined by the Society for Fetal Urology.	2	B
Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies.	2	B
Do not offer surgery as a standard for primary megaureters since most do not require surgical intervention.	2	B

3.13 **Vesicoureteric reflux**

Lack of robust prospective RCTs limits the strength of the established guidelines for the management of VUR. The scientific literature for reflux disease is still limited and the level of evidence is generally low. Most of the studies are retrospective, include different patient groups, and have poor stratification of quality. Also, there is a high risk of presenting misleading results by combining different types of studies when systematically extracting data. Therefore, for reflux disease, it is unfortunately not possible to produce recommendations based on high-quality studies. The authors have assessed the current literature, but in the absence of conclusive findings, have provided recommendations based on panel consensus. These Guidelines aim to provide a practical approach to the treatment of VUR based on risk analysis.

3.13.1 **Epidemiology, aetiology and pathophysiology**

Vesicoureteric reflux is an anatomical and/or functional disorder with potentially serious consequences, such as renal scarring, hypertension and renal failure. Fortunately, patients with VUR present with a wide range of severity, and a good proportion of reflux patients do not develop renal scars and probably do not need any intervention [541]. Vesicoureteric reflux is a very common urological anomaly in children, with an incidence of nearly 1%.

The main management goal is the preservation of kidney function, by minimising the risk of pyelonephritis. By defining and analysing the risk factors for each patient (i.e. age, sex, reflux grade, LUTD, anatomical abnormalities, and kidney status), it is possible to identify those patients with a potential risk of UTIs and renal scarring. Controversy persists over the optimal management of VUR, particularly the choice of diagnostic procedures, treatment (medical, endoscopic or surgical), and the timing of treatment.

Many children present without symptoms of UTI and, because invasive diagnostic procedures are performed only when clinically indicated, the exact prevalence of VUR is unknown. However, the prevalence of VUR in non-symptomatic children has been estimated at 0.4-1.8% [542]. Among infants prenatally identified with hydronephrosis on US, who were screened for VUR, the prevalence was 16.2% (7-35%) [543]. Siblings of children with VUR had a 27.4% (3-51%) risk of also having VUR, whereas the offspring of parents with VUR had a higher incidence of 35.7% (21.2-61.4%) [543].

However, reflux detected by sibling screening is associated with lower grades [543] and significantly earlier resolution [544]. When VUR is discovered in siblings after UTI, it is usually high-grade and associated with a high incidence of reflux nephropathy, particularly if the sibling is male and the grade of reflux was high in the index patient [545, 546].

The incidence of VUR is much higher among children with UTIs (30-50%, depending on age). UTIs are more common in girls than boys due to anatomical differences. However, among all children with UTIs, boys are more likely to have VUR than girls (29% vs. 14%). Boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve itself [547-550].

There is a clear co-prevalence between LUTD and VUR [347]. Lower urinary tract dysfunction refers to the presence of LUTS, including urge, urge incontinence, weak stream, hesitancy, frequency and UTIs, which reflect the filling and/or emptying dysfunction that may be accompanied with bowel problems [347]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [551]. A recently published Swedish reflux trial has demonstrated LUTD in 34% of patients, and subdivision into groups characteristic of children revealed that 9% had isolated overactive bladder and 24% had voiding phase dysfunction [552].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy [544]. Faster resolution of VUR is more likely with age less than one year at presentation, lower grade of reflux (grade 1-3), and asymptomatic presentation with prenatal hydronephrosis or sibling reflux. The overall resolution rate is high in congenital high-grade VUR during the first years of life. In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported at > 25%, which is higher than the resolution rate for VUR detected after infancy [552-554].

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [555-557].

Dilating VUR increases the risk of developing acute pyelonephritis and renal scarring. Untreated recurrent UTIs may have a negative impact on somatic growth and medical status of the child. Evidence of renal scarring is present in 10-40% of children with symptomatic VUR, resulting from either congenital dysplasia and/or acquired post-infectious damage, which may have a negative impact on somatic growth and general well-being [558-560].

Higher grades of VUR present with higher rates of renal scars. Scar rates vary in different patient groups. In those with prenatal hydronephrosis, renal scarring occurs in 10% of patients [561-566], whereas in patients with LUTD, this may increase up to 30% [560, 567, 568]. Renal scarring may adversely affect renal growth and function, with bilateral scarring increasing the risk of insufficiency. Reflux nephropathy (RN) may be the most common cause of childhood hypertension. Follow-up studies have shown that 10-20% of children with RN develop hypertension or end-stage renal disease [569].

3.13.2 Diagnostic evaluation

The diagnostic work-up should aim to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence of VUR, and LUT function. A basic diagnostic work-up comprises a detailed medical history (including family history, and screening for LUTD), physical examination including blood pressure measurement, urinalysis (assessing proteinuria), urine culture, and serum creatinine in patients with bilateral renal parenchymal abnormalities.

The standard imaging tests include renal and bladder US, VCUG and nuclear renal scans. The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of VUR [570]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [571, 572] (Table 7). The grading system combines two earlier classifications and is based upon the extent of retrograde filling and dilatation of the ureter, renal pelvis and calyces on VCUG [572].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [573]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [574-576]. However, despite the concerns about ionising radiation and its invasive nature, conventional VCUG still remains the gold standard because it allows better determination of the grade of VUR (in a single or duplicated kidney) and assessment of the bladder and urethral configuration.

Table 7: Grading system for VUR on VCUG, according to the International Reflux Study Committee [577]

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

Dimercaptosuccinic acid is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. Dimercaptosuccinic acid is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, Dimercaptosuccinic acid uptake is poor and appears as cold spots. Dimercaptosuccinic acid scans are therefore used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans later during follow-up [572, 578]. DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [579]. Children with a normal DMSA scan during acute UTI have a low-risk of renal damage [579].

Video-urodynamic studies are only important in patients in whom secondary reflux is suspected, such as those with spina bifida or boys in whom VCUG is suggestive of posterior urethral valves. In the case of LUTS, diagnosis and follow-up can be limited to non-invasive tests (e.g. voiding charts, US, or uroflowmetry) [347]. Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies that might influence therapy.

3.13.2.1 *Infants presenting because of prenatally diagnosed hydronephrosis*

Ultrasound of the kidney and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. It is non-invasive and provides reliable information regarding kidney structure, size, parenchymal thickness and collecting system dilatation [580, 581].

Ultrasound should be delayed until after the first week after birth because of early oliguria in the neonate. It is essential to evaluate the bladder, as well as the kidneys. The degree of dilatation in the collecting system under US, when the bladder is both full and empty, may provide significant information about the presence of VUR. Bladder wall thickness and configuration may be an indirect sign of LUTD and reflux. The absence of hydronephrosis on postnatal US excludes the presence of significant obstruction; however, it does not exclude VUR.

Monitoring with careful US avoids unnecessary invasive and irradiating examinations. The first two US scans within the first one to two months of life are highly accurate for defining the presence or absence of renal pathology. In infants with two normal, successive scans, VUR is rare, and if present it is likely to be low-grade [561, 582]. The degree of hydronephrosis is not a reliable indicator for the presence of VUR, even though cortical abnormalities are more common in high-grade hydronephrosis [543]. The presence of cortical abnormalities on US (defined as cortical thinning and irregularity, as well as increased echogenicity) warrants the use of VCUG for detecting VUR [543]. Dimercaptosuccinic acid provides more reliable and quantitative measurement of the degree of cortical abnormalities, first detected with US.

The use of VCUG is recommended in patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys with hydronephrosis, ureterocele, ureteric dilatation, and abnormal bladders, because the likelihood of VUR is much higher. In all other conditions, the use of VCUG to detect reflux is optional [543, 563, 583, 584]. When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [584]. Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive, need further evaluation to exclude obstruction.

3.13.2.2 *Siblings and offspring of reflux patients*

The screening of asymptomatic siblings and offspring is controversial. Some authors think that early identification of children with VUR may prevent episodes of UTI and therefore renal scarring, whereas others think that screening asymptomatic individuals is likely to result in significant over-treatment of clinically insignificant VUR. The overall estimate for renal cortical abnormalities is 19.3% (11-54%), with 27.8% having renal damage in cohorts of symptomatic and asymptomatic children combined. In asymptomatic siblings only, the rate of renal damage is 14.4% (0-100%). Early screening and therefore early diagnosis and treatment appears to be more effective than late screening in preventing further renal damage [543, 545, 585, 586]. The lack of RCTs for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations difficult.

3.13.2.3 *Recommendations for paediatric screening of VUR*

Recommendations	GR
Inform parents of children with vesicoureteric reflux (VUR) that siblings and offspring have a high prevalence of VUR.	A
Use renal ultrasound (US) for screening of sibling(s).	A
Use voiding cystourethrography (VCUG) if there is evidence of renal scarring on US or a history of urinary tract infection.	B
Do not screen older toilet-trained children since there is no added value in screening for VUR.	B

3.13.2.4 *Children with febrile urinary tract infections*

A routine recommendation of VCUG at zero to two years of age after the first proven febrile UTI is the safest approach as the evidence for the criteria to selecting patients for reflux detection is weak. Children with febrile infections and abnormal renal ultrasonographic findings may have higher risk of developing renal scars and they should all be evaluated for reflux [587]. If reflux is diagnosed, further evaluation has traditionally consisted of a DMSA scan.

An alternative “top-down” approach is also an option, as suggested by several studies in the literature. This approach carries out an initial DMSA scan close to the time of a febrile UTI, to determine the presence of pyelonephritis, which is then followed by VCUG if the DMSA scan reveals kidney involvement. A normal DMSA scan with no subsequent VCUG will fail to spot VUR in 5-27% of cases, with the missed VUR presumably being less significant. In contrast, a normal DMSA scan with no VCUG avoids unnecessary VCUG in > 50% of those screened [341, 588-590].

3.13.2.5 *Children with lower urinary tract symptoms and vesicoureteric reflux*

Detection of LUTD is essential in treating children with VUR. It is suggested that reflux with LUTD resolves faster after LUTD correction, and that patients with LUTD are at higher risk for developing UTI and renal scarring [552, 591]. The co-existence of both conditions should be explored in any patient who has VUR. If there are symptoms suggestive of LUTD (e.g. urgency, wetting, constipation or holding manoeuvres), an extensive history and examination, including voiding charts, uroflowmetry and residual urine determination, will reliably diagnose underlying LUTD.

In LUTD, VUR is often low-grade and US findings are normal, and there is no indication for performing VCUG in all children with LUTD, but the presence of febrile infections should be meticulously investigated. The co-existence of LUTD and VUR means it would be better to do a test covering both conditions, such as a videourodynamic study (VUDS). Any patient with LUTD and a history of febrile UTI should be investigated with a VUDS, if available. Furthermore, any child who fails standard therapy for LUTD should undergo urodynamic investigation. At this stage, combining a urodynamic study with VCUG is highly recommended.

3.13.3 **Disease management**

There are two main treatment approaches: conservative (non-surgical) and surgical.

3.13.3.1 *Non-surgical therapy*

The objective of conservative therapy is prevention of febrile UTI. It is based on the understanding that:

- VUR resolves spontaneously, mostly in young patients with low-grade reflux. Resolution is nearly 80% in VUR grades I and II and 30-50% in VUR grades III-V within four to five years of follow-up. Spontaneous resolution is low for bilateral high-grade reflux [592].
- VUR does not damage the kidney when patients are free of infection and have normal LUT function.
- There is no evidence that small scars can cause hypertension, renal insufficiency or problems during pregnancy. Indeed, these are possible only in cases of severe bilateral renal damage.
- The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with LUTD [567, 591, 593-595].
- Circumcision during early infancy may be considered as part of the conservative approach because it is effective in reducing the risk of infection in normal children [596].

3.13.3.1.1 Follow-up

Regular follow-up with imaging studies (e.g. VCUG, nuclear cystography, or DMSA scan) is part of the conservative management to monitor spontaneous resolution and kidney status. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

3.13.3.1.2 Continuous antibiotic prophylaxis

Vesicoureteral reflux increases the risk of UTI and renal scarring especially when in combination with LUTD. Many prospective studies have evaluated the role of continuous antibiotic prophylaxis in the prevention of recurrent UTI and renal scarring.

It is clear that antibiotic prophylaxis may not be needed in every reflux patient [567, 597-599]. Trials show the benefit of CAP is none or minimal in low-grade reflux. Continuous antibiotic prophylaxis is useful in patients with grade III and IV reflux in preventing recurrent infections but its use in preventing further renal damage is not proven. Toilet-trained children and children with LUTD derive much better benefit from CAP [371-374, 600, 601]. The RIVUR trial was the largest, randomised, placebo-controlled, double blind, multi-centre study, involving 607 children aged 2-72 months with grade I-IV VUR. The RIVUR study showed

that prophylaxis reduced the risk of recurrent UTI by 50% but not renal scarring and its consequences (hypertension and renal failure), at the cost of increased antimicrobial resistance. The benefit of prophylaxis was insignificant in patients with grade III or IV VUR and in the absence of LUTD [376, 602-604].

It may be difficult and risky to select patients who do not need CAP. A safe approach would be to use CAP in most cases. Decision-making may be influenced by the presence of risk factors for UTI, such as young age, high-grade VUR, status of toilet-training/LUTS, female sex, and circumcision status. Although the literature does not provide any reliable information about the duration of CAP in reflux patients, a practical approach would be to use CAP until after children have been toilet-trained and ensuring that there is no LUTD. CAP is mandatory in patients with LUTD and reflux. Active surveillance of UTI is needed after CAP is discontinued. The follow-up scheme and the decision to perform an anti-reflux procedure or discontinuation of CAP may also depend on personal preferences and the attitude of patients and parents. It is strongly advised that the advantages and disadvantages should be discussed in detail with the family.

3.13.3.2 Surgical treatment

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral reimplantation.

3.13.3.2.1 Subureteric injection of bulking materials

With the availability of biodegradable substances, endoscopic subureteric injection of bulking agents has become an alternative to long-term antibiotic prophylaxis and open surgical intervention in the treatment of VUR in children. Using cystoscopy, a bulking material is injected beneath the intramural part of the ureter in a submucosal location. The injected bulking agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, which prevents reflux of urine into the ureter, while still allowing its antegrade flow.

Several bulking agents have been used over the past two decades, including polytetrafluoroethylene (PTFE or Teflon), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, a solution of dextranomer/hyaluronic acid (Deflux, Dexell) and more recently polyacrylate-polyalcohol copolymer hydrogel (Vantris) [605, 606].

Although the best results have been obtained with PTFE [607], due to concerns about particle migration, PTFE has not been approved for use in children [608]. Although they are all biocompatible, other compounds such as collagen and chondrocytes have failed to provide a good outcome. Deflux was approved by the USA FDA in 2001 for the treatment of VUR in children. Initial clinical trials have demonstrated that this method is effective in treating reflux [609]. Studies with long-term follow-up have shown that there is a high recurrence rate which may reach as high as 20% in two years [597].

In a meta-analysis [610] of 5,527 patients and 8,101 renal units, the reflux resolution rate (by ureter) following one treatment for grades I and II reflux was 78.5%, 72% for grade III, 63% for grade IV, and 51% for grade V. If the first injection was unsuccessful, the second treatment had a success rate of 68% and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was significantly lower for duplicated (50%) vs. single (73%) systems, and neuropathic (62%) vs. normal (74%) bladders.

Clinical validation of the effectiveness of anti-reflux endoscopy is currently hampered by the lack of methodologically appropriate studies. In the most recent prospective, randomised trials comparing three treatment arms: i) endoscopic injection; ii) antibiotic prophylaxis; iii) surveillance without antibiotic prophylaxis in 203 children aged one to two years with grade III/IV reflux, endoscopic treatment gave the highest resolution rate of 71% compared to 39% and 47% for treatment arms ii and iii, respectively, after two years' follow-up. The recurrence rate at two years after endoscopic treatment was 20%. The occurrence of febrile UTIs and scar formation was highest in the surveillance group at 57% and 11%, respectively. New scar formation rate was higher with endoscopic injection (7%) compared with antibiotic prophylaxis (0%) [611]. Longer follow-up studies are needed to validate these findings.

3.13.3.2.2 Open surgical techniques

Various intra- and extravesical techniques have been described for the surgical correction of reflux. Although different methods have specific advantages and complications, they all share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter. All techniques have been shown to be safe with a low rate of complications and excellent success rates (92-98%) [612].

The most popular and reliable open procedure is cross trigonal re-implantation described by Cohen. The main concern with this procedure is the difficulty of accessing the ureters endoscopically if needed when the child is older. Alternatives are suprahiatal re-implantation (Politano-Leadbetter technique) and infrahiatal re-implantation (Glenn-Anderson technique). If an extravesical procedure (Lich-Gregoir) is planned, cystoscopy should be performed pre-operatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical antireflux procedure may be considered, because

simultaneous bilateral extravesical reflux repair carries an increased risk of temporary post-operative urine retention [613]. Overall, all surgical procedures offer very high and similar success rates for correcting VUR.

3.13.3.2.3 Laparoscopy and robot-assisted

There have been a considerable number of case series of transperitoneal extravesical and pneumovesicoscopic intravesical ureteral reimplantation, which have shown the feasibility of the techniques. Various anti-reflux surgeries have been performed with the robot and the extravesical approach is the most commonly used. Although initial reports give comparable outcomes to their open surgical counterparts in terms of successful resolution of reflux, further studies are needed to define the success rates, costs and benefits of this minimal invasive approach [614, 615].

The major shortcoming of the new techniques seems to be the longer operative times, which hinder their wider acceptance. Also, laparoscopic or robotic assisted approaches are more invasive than endoscopic correction and their advantages over open surgery are still debated. Therefore, at present, a laparoscopic approach cannot be recommended as a routine procedure. It can be offered as an alternative to the parents in centres where there is established experience [596, 614, 616-623].

3.13.4 **Summary of evidence and recommendations for the management of vesicoureteric reflux in childhood**

Summary of evidence	LE
There is no evidence that correction of persistent low-grade reflux (grades I-III) without symptoms and normal kidneys offers a significant benefit.	4
The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation needs to be challenged, because the treatment should be tailored to different risk groups.	2
Surgical correction should be considered in patients with persistent high-grade reflux (grades IV/V). There is no consensus about the timing and type of surgical correction. The outcome of open surgical correction is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades.	2
The choice of management depends on the presence of renal scars, clinical course, grade of reflux, ipsilateral renal function, bilaterality, bladder function, associated anomalies of the urinary tract, age, compliance, and parental preference. Febrile UTI, high-grade reflux, bilaterality, and cortical abnormalities are considered to be risk factors for possible renal damage. The presence of LUTD is an additional risk factor for new scars.	2

Recommendations	GR
Initially treat all patients diagnosed within the first year of life with continuous antibiotic prophylaxis, regardless of the grade of reflux or presence of renal scars.	C
Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	A
Offer definitive surgical or endoscopic correction to patients with frequent breakthrough infections.	A
Offer surgical correction to patients with persistent high-grade reflux (grades IV/V) if intervention is needed; the outcome of open surgical correction is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades.	B
Initially manage all children presenting at age one to five years conservatively.	B
Offer surgical repair to children presenting with high-grade reflux or abnormal renal parenchyma.	B
Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	B
Ensure that a detailed investigation for the presence of lower urinary tract dysfunction (LUTD) is done in all children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.	A
Consider surgical correction, if parents prefer definitive therapy to conservative management. Endoscopic treatment is an option for all children with low grades of reflux.	B

Select the most appropriate management option based on : <ul style="list-style-type: none"> • the presence of renal scars; • clinical course; • the grade of reflux; • ipsilateral renal function; • bilaterality; • bladder function; • associated anomalies of the urinary tract; • age and gender; • compliance; • parental preference. 	A
In high-risk patients who already have renal impairment, a more aggressive, multi-disciplinary approach is needed.	A

Table 8: Management and follow-up according to different risk groups

Risk Groups	Presentation	Initial treatment	Comment	Follow-up
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grades IV-V), abnormal kidneys and LUTD	Initial treatment is always for LUTD with CAP; intervention may be considered in cases of BT infections or persistent reflux	Greater possibility of earlier intervention	More aggressive follow-up for UTI and LUTD; full re-evaluation after 6 months
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD	Intervention should be considered	Open surgery has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed		Follow-up for UTI, LUTD, and kidney status until after puberty

Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

BT = breakthrough; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction; PNH = prenatal diagnosed hydronephrosis; UTI = urinary tract infection; VCUG = voiding cystourethrography.

3.14 Urinary stone disease

3.14.1 *Epidemiology, aetiology and pathophysiology*

Paediatric stone disease is an important clinical problem in paediatric urology practice. Because of its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. Obtaining a stone-free state with close follow-up are of the utmost importance, although, it may not be possible in some circumstances (e.g. oxalosis or nephrocalcinosis).

However, bladder stones are still common in underdeveloped areas of the world and are usually ammonium acid urate and uric acid stones, strongly implicating dietary factors [624]. Patients with augmented bladder constitute another important group with a risk of up to 15% [625].

The incidence and characteristics of stones show a wide geographical variation in children. Although urinary stone disease is generally considered to be a relatively rare disease, it is quite common in some parts of the world. Paediatric stone disease is endemic in Turkey, Pakistan and in some South Asian, African and South American states. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western world [626-628], especially in girls, Caucasian ethnicity, African Americans and older children [629]. More than 70% of stones in children contain calcium oxalate, while infection stones are found more frequently in younger children [630].

3.14.2 *Classification systems*

Urinary stone formation is the result of a complex process involving metabolic, anatomical factors and presence of infection.

3.14.2.1 *Calcium stones*

Calcium stones are usually made from calcium oxalate or calcium phosphate. Super-saturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia) or magnesium (hypomagnesemia) play a major role in the formation of calcium oxalate stones.

Hypercalciuria: This is defined by a 24-hour urinary calcium excretion of more than 4 mg/kg/day (0.1 mmol/kg/day) in a child weighing < 60 kg. In infants younger than three months, 5 mg/kg/day (0.125 mmol/kg/day) is considered to be the upper limit for normal calcium excretion [631].

Hypercalciuria can be classified as either idiopathic or secondary. Idiopathic hypercalciuria is diagnosed when clinical, laboratory, and radiographic investigations fail to delineate an underlying cause leading to hypercalcaemia. Urinary calcium may increase in patients with high sodium chloride intake. Secondary hypercalciuria occurs when a known process produces excessive urinary calcium. In secondary (hypercalcemic) hypercalciuria, a high serum calcium level may be due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilisation, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) [632].

A good screening test for hypercalciuria compares the ratio of urinary calcium to creatinine. The normal calcium-to-creatinine ratio in children is less than 0.2. If the calculated ratio is higher than 0.2, repeat testing is indicated. Neonates and infants have a higher calcium excretion and lower creatinine excretion than older children [631, 632]. If the follow-up ratios are normal, then no additional testing for hypercalciuria is needed.

However, if the ratio remains elevated, a timed 24-hour urine collection should be obtained and the calcium excretion calculated.

The 24-hour calcium excretion test is the standard criterion for the diagnosis of hypercalciuria. If calcium excretion is higher than 4 mg/kg/day (0.1 mmol/kg/day), the diagnosis of hypercalciuria is confirmed and further evaluation is warranted: levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, phosphorus, magnesium, pH, and parathyroid hormone. Freshly voided urine should be measured for pH [631-634]. In addition to calcium, the 24-hour urine analysis should also include phosphorus, sodium, magnesium, uric acid, citrate and oxalate.

Initial management is always to increase fluid intake and urinary flow. Dietary modification is a mandatory part of effective therapy. The child should be referred to a dietician to assess accurately the daily intake of calcium, animal protein, and sodium. Dietary sodium restriction is recommended as well as maintenance of calcium intake consistent with the daily needs of the child [635]. A brief trial of a low-calcium diet can be carried out to determine if exogenous calcium intake and/or calcium hyperabsorption is contributing to high urinary calcium. Any recommendation to restrict calcium intake below the daily needs of the child should be avoided. Moreover, low calcium intake is a risk factor for stone formation [636] (LE: 3).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat idiopathic hypercalciuria, especially with calcium renal leak, at a starting dosage of 0.5-1 mg/kg/day [637-640] (LE: 3). In long-term use of thiazide-type diuretics, a decrease in hypocalciuric effect may be seen after the third month and may cause hypokalemia, hypocitraturia, hyperuricaemia and hypomagnesaemia. Therefore, control of blood and serum values should be performed with regular intervals. Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies [637, 641] (LE: 4).

Hyperoxaluria: Only 10-15% of oxalate comes from diet.

The average child excretes less than 50 mg (0.57 mmol)/1.73 m²/day [642-644], while infants excrete four times as much. Hyperoxaluria may result from increased dietary intake, enteric hyperabsorption (as in short bowel syndrome) or an inborn error of metabolism.

In rare primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue in resulting deposition of calcium oxalate in other tissues (oxalosis). The diagnosis is made upon laboratory findings of severe hyperoxaluria and clinical symptoms. The definitive diagnosis requires liver biopsy to assay the enzyme activity.

Other forms of hyperoxaluria, as mentioned earlier, may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Yet, the majority of children have 'mild' (idiopathic) hyperoxaluria, with urine oxalate levels elevated only mildly in these cases. The treatment of hyperoxaluria consists of the promotion of high urine flow, restriction of dietary oxalate and regular calcium intake. Pyridoxine may be useful in reducing urine levels, especially in primary hyperoxaluria. Citrate administration increases inhibitory urine activity [637, 645] (LE: 4).

Hypocitraturia: Citrate is a urinary stone inhibitor. Citrate acts by binding to calcium and by directly inhibiting the growth and aggregation of calcium oxalate as well as calcium phosphate crystals. Thus low urine citrate may be a significant cause of calcium stone disease. In adults, hypocitraturia is the excretion of citrate in urine of less than 320 mg/day (1.5 mmol/day) for adults; this value must be adjusted for children depending on body size [646-648].

Hypocitraturia usually occurs in the absence of any concurrent symptoms or any known metabolic derangements. It may also occur in association with any metabolic acidosis, distal tubular acidosis or diarrhoeal syndromes.

Environmental factors that lower urinary citrate include a high protein intake and excessive salt intake. Many reports emphasise the significance of hypocitraturia in paediatric calcium stone disease. The presence of hypocitraturia ranges from 30% to 60% in children with calcium stone disease [648, 649].

The restoration of normal citrate levels is advocated to reduce stone formation, although there are few relevant studies in children. Hypocitraturia is treated by potassium citrate at a starting dose of 1 mEq/kg, given in two divided doses [647] (LE: 3). The side effects of potassium citrate are very rare and most of the time they include non-specific gastrointestinal complaints. Potassium citrate should be used with caution in hyperkalemic and chronic renal failure conditions.

3.14.2.2 *Uric acid stones*

Uric acid stones are responsible for urinary calculi in 4-8% of children. Uric acid is the end product of purine metabolism. Hyperuricosuria is the main cause of uric acid stone formation in children. A daily output of uric acid of more than 10 mg/kg/day (0,6 mmol/kg/day) is considered to be hyperuricosuria [637].

The formation of uric acid stones is mainly dependent on the presence of acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at pH of < 5.8. As the pH becomes more alkaline, uric acid crystals become more soluble and the risk of uric acid stone formation is reduced.

In the familial or idiopathic form of hyperuricosuria, children usually have normal serum uric acid levels. In other children, it can be caused by uric acid overproduction secondary to inborn errors of metabolism, myeloproliferative disorders or other causes of cell breakdown. Hyperuricosuria is also caused by high purine and protein intake. Although hyperuricosuria is a risk factor for calcium oxalate stone formation in adults, this does not appear to be a significant risk factor in children.

Uric acid stones are non-opaque stones. Plain X-rays are insufficient to show uric acid stones, and renal sonography and spiral CT are used for diagnosis.

Alkalinisation of urine is the mainstay of therapy and prevention for uric acid stones. Citrate preparations are useful as alkalinising agents. Maintaining a urine pH of 6 to 6.5 is sufficient to prevent uric acid stones [637]. In cases who failed with conservative measures with sustaining hyperuricosuria and hyperuricemia, stone recurrences or myeloproliferative diseases, allopurinol (10 mg/kg) may be used. This medication may cause several drug reactions (rash, diarrhoea, eosinophilia) and should be cautiously used in chronic renal failure patients.

3.14.2.3 *Cystine stones*

Cystinuria is the cause of cystine stone formation and accounts for 2-6% of all urinary stones in children. Cystinuria is an incompletely recessive autosomal disorder characterised by failure of renal tubules to reabsorb four basic amino acids: cystine, ornithine, lysine and arginine.

Of these four amino acids, only cystine has poor solubility in urine, so that only cystine stones may form in the case of excessive excretion in urine. Cystine solubility is pH-dependent, with cystine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones. Cystine stones are faintly radiopaque and may be difficult to visualise on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shockwave lithotripsy (SWL).

The medical treatment for cystine stones aims to reduce cystine saturation in urine and increase its solubility. The initial treatment consists of maintaining a high urine flow and the use of alkalinising agents, such as potassium citrate to maintain urine pH at above 7.0 (better above 7.5). If this treatment fails, the use of alphamercaptopropionyl glycine or D-penicilamin may increase cystine solubility and reduce cystine levels in urine and prevent stone formation. Side effects of these drugs are mostly mild and include gastrointestinal complaints (alterations in taste and odour), fever and rash, however they can be associated with severe side effects, such as bone marrow depression, nephrotic syndrome and epidermolysis [650] (LE: 4).

3.14.2.4 *Infection stones (struvite stones)*

Infection-related stones constitute nearly 5% of urinary stones in children, though incidence increases over 10% in younger ages [651] and in non-endemic regions [630, 652]. Bacteria capable of producing urease enzyme (Proteus, Klebsiella, Pseudomonas) are responsible for the formation of such stones.

Urease converts urea into ammonia and bicarbonate, alkalinising the urine and further converting bicarbonate into carbonate. In the alkaline environment, triple phosphates form, eventually resulting in a supersaturated environment of magnesium ammonium phosphate and carbonate apatite, which in turn leads to stone formation.

In addition to bacterial elimination, stone elimination is essential for treatment, as stones will harbour infection and antibiotic treatment will not be effective. Consideration should be given to investigating any congenital problem that causes stasis and infection. Genitourinary tract anomalies predispose to formation of such stones.

3.14.3 **Diagnostic evaluation**

Presentation tends to be age-dependent, with symptoms such as flank pain and haematuria being more common in older children. Non-specific symptoms (e.g. irritability, vomiting) are common in very young children. Haematuria, usually visible, occurring with or without pain, is less common in children. However, non-visible haematuria may be the sole indicator and is more common in children. In some cases, urinary infection may be the only finding leading to radiological imaging in which a stone is identified [653, 654].

3.14.3.1 *Imaging*

Generally, US should be used as a first study. Renal US is very effective for identifying stones in the kidney. Many radiopaque stones can be identified with a simple abdominal flat-plate examination. The most sensitive test for identifying stones in the urinary system (especially for ureteric stones) is non-contrast helical CT scanning. It is safe and rapid, with 97% sensitivity and 96% specificity [655-657] (LE: 2). Despite its high diagnostic accuracy, because of the potential radiation hazards, its use should be reserved for cases with non-informative US and/or plain abdominal roentgenogram. Low dose protocols have also been developed with the goal of reducing radiation dose with adequate image quality [658]. Intravenous pyelography is rarely used in children, but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

3.14.3.2 *Metabolic evaluation*

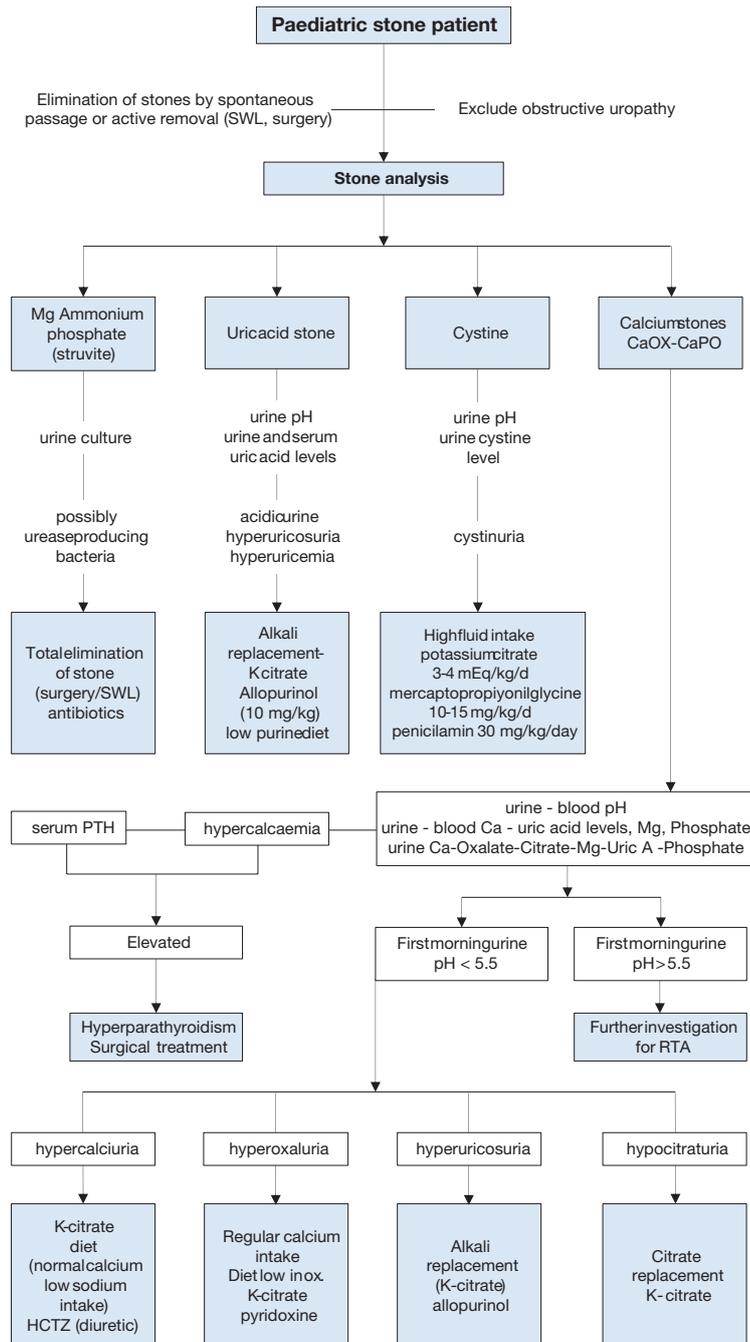
Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with urinary stone should be given a complete metabolic evaluation [624, 659-661].

Metabolic evaluation includes:

- family and patient history of metabolic problems and dietary habits;
- analysis of stone composition (following stone analysis, metabolic evaluation can be modified according to the specific stone type);
- electrolytes, blood/urea/nitrogen (BUN), creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, carbonate, albumin, and parathyroid hormone (if there is hypercalcaemia);
- spot urinalysis and culture, including ratio of calcium to creatinine;
- urine tests, including a 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, protein, and creatinine clearance;
- 24-hour cystine analysis if cystinuria is suspected (positive sodium nitroprusside test, cystine stone, cystine hexagonal crystals in urine).

Figure 8 provides an algorithm of how to perform metabolic investigations in urinary stone disease in children and how to plan medical treatment accordingly.

Figure 8: Algorithm for metabolic investigations in urinary stone disease in children



Ca = calcium; HCTZ = hydrochlorothiazide; Mg = magnesium; Ox = oxalate; PTH = parathyroid hormone; SWL = extracorporeal shockwave lithotripsy; RTA = renal tubular acidosis; Uric-A = uric acid.

3.14.4 Management

With the advance of technology stone management has changed from open surgical approaches to endoscopic techniques that are less invasive. Deciding the type of treatment depends on the number, size, location, stone composition and the anatomy of the urinary tract [659, 662, 663]. Expectant management is the initial management in children with asymptomatic small size stones (< 4-5 mm) with a possibility of spontaneous clearance. There is no consensus on the size of stones for different ages eligible for clearance and the duration of conservative follow-up. Adult literature reveals the benefits of medical expulsive therapy (MET) using α -blockers. Although, experience in children is limited showing different results [664], a recent meta-analysis of three randomised and two retrospective studies demonstrate that treatment with MET results in increased odds of spontaneous ureteral stone passage and a low rate of adverse events [665]. Currently, most paediatric stones can easily be managed by shockwave lithotripsy (SWL). Endoscopic treatment can be applied for ureteric and bladder stones. Percutaneous removal of stones is also possible for kidney stones in

children. Only a small portion of children will require open surgery but all attempts must be made to completely remove all stones since post-operative residual fragments pass spontaneously in only 20-25% of cases [666, 667]. A congenital obstructive uropathy should be managed together with stone removal therapy to prevent recurrence.

3.14.4.1 *Extracorporeal shockwave lithotripsy*

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney [668-675].

The mean number of shockwaves for each treatment is approximately 1,800 and 2,000 (up to 4,000 if needed) and the mean power settings vary between 14 kV and 21 kV. The use of US and digital fluoroscopy has significantly decreased the radiation exposure and it has been shown that children are exposed to significantly lower doses of radiation compared to adults [662, 676, 677]. Concerns about anaesthesia no longer present a problem due to advances in technique and medication, even in the infant age group. The type of anaesthesia should be general or dissociative for children under ten years of age, whereas conventional intravenous sedation or patient-controlled analgesia is an option for older children who are able to co-operate [678] (LE: 2b).

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and re-treatment rate increases. The stone-free rates for < 1 cm, 1-2 cm, > 2 cm and overall, were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases [662, 676, 677, 679-683].

Localisation of the calculi has been described as a significant factor affecting the success rates in different studies. Stones in the renal pelvis and upper ureter seem to respond better to SWL. For these locations, the stone clearance rates are nearly 90%. However, SWL was found to be less effective for caliceal stones particularly the lower caliceal stones. Several studies reported stone-free rates for isolated lower caliceal stones varying between 50% and 62% [684-687].

Shockwave lithotripsy can also be used to treat ureteral calculi. However, this is a more specific issue and controversial. The success rates with SWL are less for distal ureteric stones. There may also be technical problems with localisation and focusing of ureteric stones in children [684-686, 688, 689].

The type of machine used has a strong effect on success rates and complications. First-generation machines can deliver more energy to a larger focal zone, resulting in higher fragmentation rates in a single therapy. However, general anaesthesia is usually required due to the intolerable discomfort associated with a first-generation machine. Later-generation machines have a smaller focal zone and deliver less energy, and have a lower risk of pulmonary trauma, however, additional treatments may be needed. The success rate is higher in younger children [682].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient [681, 682]. Stenting is essential in solitary kidneys undergoing SWL treatment. Children with a large stone burden have a high risk of developing Steinstrasse and urinary obstruction and should be followed more closely for the risk of prolonged urinary tract obstruction after SWL. Post-SWL stent or nephrostomy tube placement may be needed in prolonged obstruction [660, 683].

The Hounsfield Unit (HU) of stone on noncontrast tomography has also been shown to be a predictive factor for success in children and SWL was found to be more successful in stones with HU less than 600 [667] and 1000 [690]. Two nomogram studies revealed male gender, younger age, smaller stone size, single stone, non-lower pole localisation and negative history for previous intervention are favourable factors for stone clearance in paediatric SWL [691, 692].

Complications arising from SWL in children are usually self-limiting and transient. The most common are:

- renal colic;
- transient hydronephrosis;
- dermal ecchymosis;
- UTI;
- formation of Steinstrasse;
- sepsis;
- rarely, haemoptysis.

In children with sterile pre-operative urine cultures, antibiotic prophylaxis to decrease infectious complications is not recommended [693]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PNL).

Because of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [694-703].

3.14.4.2 Percutaneous nephrolithotomy (PCNL)

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery should be used for larger and complex stones. Pre-operative evaluation, indication and surgical technique are similar in children and adults. In most cases, PCNL is used as monotherapy, but is also used as an adjunctive procedure to other therapies.

The use of adult-sized instruments, in association with an increased number of tracts and sheath size, seems to increase blood loss. However, the development of small-calibre instruments means that PCNL can be used in children. In children (particularly smaller children), PCNL has some advantages, such as smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length, and lower cost [693, 704, 705].

As monotherapy, PCNL is considerably effective and safe. The reported stone-free rates in the recent literature are between 86.9% and 98.5% after a single session. These rates increase with adjunctive measures, such as second-look PCNL, SWL and URS. Even in complete staghorn cases, a clearance rate of 89% has been achieved following a single session [694, 706-710].

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion in the modern series is reported in less than 10% [711-716] and is closely associated with stone burden, operative time, sheath size and the number of tracts [711, 717, 718]. In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% [711-713, 715, 716, 719] and the origin of fever is not always found to be the infection. With the availability of smaller size instruments, miniaturised PCNL ('miniperc') through a 13F or 14F sheath [704, 720, 721] as well as ultramini-PCNL (UMP) through 12F sheaths [722] have become possible, with decreased transfusion rates [720]. This miniaturisation has been further developed into the technique of 'micro-perc' using a 4.85F 'all-seeing needle'. This technique is still experimental and enables the stone to be fragmented by a laser *in situ* and left for spontaneous passage [723]. A recent study revealed that microperc provides a similar stone-free rate with similar complication rates and a lower additional treatment rate compared with SWL in the treatment of kidney stone disease in children [724] (LE: 3, GR: B). For stones 10-20 mm, micro-PNL was shown to have comparable results, with lesser bleeding, compared to mini-PCNL [725] (LE: 3, GR: B). As experience has accumulated in adult cases, new approaches have also started to be applied in children, including tubeless PCNL. This technique has been used in uncomplicated surgery for stones smaller than 2 cm, with patients left either with an indwelling catheter or double J stent in the ureter [714, 719] or totally tubeless [726]. Moreover, use of ultrasonography for establishment of access [727] and supine approach [728] were also reported to be feasible in children.

The mean post-operative hospital stay is similar to adults. It is reported as three to four days in all published literature and is much shorter than open surgery. The less invasive nature of this technique has made it a promising alternative to open surgery for treating renal stones in children (LE: 2; GR:B) [713-728].

3.14.4.3 Ureterorenoscopy

The increasing availability of smaller size endourological equipment has made it possible to manage paediatric ureteral stones using endoscopic techniques.

The technique used in children is similar to the one used in adults. It is strongly recommended that guide wires are used and the procedure is performed using direct vision. Routine balloon dilation of ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is being performed much less and only in selected cases. There is a tendency to use hydrodilation more because it is similarly effective [693, 695, 696, 729-732] (LE: 3; GR: B).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Because of the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [694-703].

All studies reporting the use of endoscopy for ureteric stones in children have clearly demonstrated that there is no significant risk of ureteric strictures or reflux with this mode of therapy (LE: 1; GR: A). The risk of post-operative hydronephrosis depends on the presence of impacted stone and ureteral injury during operation [733]. A multi-institutional study on the use of semi-rigid ureteroscopy for ureteral calculi in children has revealed that the procedure is effective with a 90% stone-free rate and efficacy quotient. The study also focused on the factors affecting the complication rates. The authors found that although operating time, age, institutional experience, orifice dilation, stenting and stone burden were significant on univariate analysis, multivariate analysis revealed that operating time was the only significant parameter affecting the complication rate [734].

A recent literature review contains a growing number of case series on the use of flexible ureterorenoscopic interventions in children. Both intrarenal and ureteric stones can be treated using this approach [735-739]. In these series, the authors generally did not use active orifice dilation, but attempted to

use a ureteral sheath where possible. However, an important problem was the inability to obtain retrograde access to the ureter in approximately half of the cases [736, 737]. This problem can be overcome by stenting and leaving the stent indwelling for passive dilation of the orifice, and performing the procedure in a second session. The success rates varied between 60 and 100%, with a negligible number of complications [735, 737-740]. The need for additional procedures was related to stone size [739]. A comparative study showed that retrograde intrarenal surgery (RIRS) had similar stone-free rate compared to ESWL after three months, with fewer sessions [741], however for stones larger than 2 cm, RIRS monotherapy has lower stone-free rates than mini-PCNL with the advantages of decreased radiation exposure, fewer complications and shorter hospital stay [742] (LE: 3; GR: B). On the other hand, for stones between 10-20 mm, RIRS has similar success and complication rates and shorter hospital stay and low radiation exposure when compared to micro-PNL [743] (LE: 3; GR: B).

3.14.4.4 *Open or laparoscopic stone surgery*

Most stones in children can be managed by SWL and endoscopic techniques. However, in some situations, open surgery is inevitable. Good candidates for open stone surgery include very young children with large stones and/or a congenitally obstructed system, which also require surgical correction. Open surgery is also necessary in children with severe orthopaedic deformities that limit positioning for endoscopic procedures.

In centres with a well-established experience, a laparoscopic approach may be a good alternative for some cases as a last resort before open surgery. Suitable candidates include patients who have a history of previous failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant UPJ obstruction or caliceal diverticula, megaureter, or large impacted stones. Laparoscopic stone surgery via conventional or a robot-assisted transperitoneal or retroperitoneal approach can be attempted. However, there is very limited experience with these techniques and they are not routine therapeutic modalities [744-747].

Bladder stones in children can usually be managed by endoscopic techniques. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem.

In addition to advantage and disadvantage of each treatment modality for the specific size and location of the stone, one will have to consider the availability of the instruments and the experience with each treatment modality before the choice of technique. Recommendations for interventional management are given in Table 9.

Table 9: Recommendations for interventional management in paediatric stones

Stone size and localisation*	Primary treatment option	LE	GR	Secondary treatment options	Comment
Staghorn stones	PCNL	2b	B	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10 mm	SWL	2b	B	RIRS/PCNL/MicroPerc	
Pelvis 10-20 mm	SWL	2b	B	PCNL/RIRS/MicroPerc/Open	Multiple sessions with SWL may be needed. PCNL has similar recommendation grade.
Pelvis > 20 mm	PCNL	2b	B	SWL/Open	Multiple sessions with SWL may be needed.
Lower pole calyx < 10 mm	SWL	2b	B	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
Lower pole calyx > 10 mm	PCNL	2b	B	SWL/ MicroPerc	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	2b	B	PCNL/URS/Open	
Lower ureteric stones	URS	2a	A	SWL/Open	Additional intervention need is high with SWL.
Bladder stones	Endoscopic	2b	B		Open is easier and with less operative time with large stones.

* Cystine and uric acid stones excluded.

PCNL = percutaneous nephrolithostomy; SWL = shockwave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

3.14.5 Summary of evidence and recommendations for the management of urinary stones

Summary of evidence	LE
The incidence of stone disease in children is increasing.	2
Contemporary surgical treatment is based on minimally invasive modalities. Open surgery is very rarely indicated.	2a
The term 'clinically insignificant residual fragments' is not appropriate for children since most of them become symptomatic and require intervention.	2b

Recommendations	LE	GR
Use plain abdominal X-ray and ultrasound (US) as the primary imaging techniques for the diagnosis and follow-up of stones.	2b	B
Use low-dose non-contrast computed tomography (CT) in cases with a doubtful diagnosis, especially of ureteral stones or complex cases requiring surgery.	2a	B
Perform a metabolic and anatomical evaluation in any child with urinary stone disease.	2a	B
Any kind of interventional treatment should be supported with medical treatment for the underlying metabolic abnormality, if detected.	2a	B
Open surgery may be done under circumstances in which the child is very young with large stones, in association with congenital problems requiring surgical correction and/or with severe orthopedic deformities that limit positioning for endoscopic procedures.	2a	B
Use appropriately-sized instruments in order to decrease the number of complications during surgical treatment.	2b	B

3.15 Obstructive pathology of renal duplication: ureterocele and ectopic ureter

3.15.1 *Epidemiology, aetiology and pathophysiology*

Ureterocele and ectopic ureter are the two main anomalies associated with complete renal duplication, but they also occur in a single system. At present, antenatal US detects both conditions in the majority of cases if associated with obstruction, and diagnosis is confirmed after birth by further examination. Later in life, these anomalies are revealed by clinical symptoms: UTI, pain, calculus formation, disturbances of micturition, and urinary incontinence. There is a wide variation of symptoms in patients with ureterocele (from the asymptomatic patient to urosepsis, urinary retention and upper tract dilatation after birth).

3.15.1.1 *Ureterocele*

Ureterocele is 4-7 times more frequent in female than in male patients; the overall incidence in autopsies is around one in 4,000 children. Around 80% is associated with the upper pole ureter in duplicated systems and 20% in single systems. About 10% of ureteroceles are bilateral [748].

3.15.1.2 *Ectopic ureter*

Ectopic ureter is less frequent than ureterocele (10 in 19,046 autopsies), but is also more common in female patients (male to female ratio, 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine [749]. Eighty per cent of ectopic ureters are associated with complete renal duplication; however, in male patients about 50% of ectopic ureters are associated with a single system [750].

3.15.2 *Classification systems*

3.15.2.1 *Ureterocele*

Ureterocele is a cystic dilatation that develops in the intravesical part of the submucosal ureter. The aetiology remains unclear [751-753]. A single-system ureterocele is associated with a kidney with one ureter, and in duplex systems, the ureterocele belongs to the upper pole.

Ureteroceles usually cause obstruction of the upper pole, but the degree of obstruction and functional impairment is variable according to the type of ureterocele and upper pole dysplasia. In the orthotopic form, there is often no or only mild obstruction, and frequently the function of the moiety is normal or slightly impaired, and the corresponding ureter may be dilated. Cystic renal dysplasia is also associated with a single system ureterocele [754, 755]. Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [756]. In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional [757, 758]. The corresponding ureter is a mega-ureter. In the caeco-ureterocele (see definition below), the upper pole of the renal duplication is dysplastic and non-functional.

3.15.2.1.1 *Ectopic (extravesical) ureterocele*

If any portion of the ureterocele extends into the bladder neck or urethra, it is called an ectopic ureterocele. Ectopic ureterocele is the most common form of ureterocele (> 80%). It can be voluminous, dissociating the trigone and slipping into the urethra, and may prolapse through the urethral meatus (caeco-ureterocele). The ureterocele orifice is tight, and located in the bladder itself or below the neck. The ureter corresponding to the lower pole moiety is raised by the ureterocele and is frequently refluxing or compressed by the ureterocele, leading to an obstructive megaureter. A contralateral renal duplication is associated in 50% of cases. Occasionally, large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract.

3.15.2.1.2 *Orthotopic (intravesical) ureterocele*

The intravesical or orthotopic ureterocele is completely located in the bladder. Intravesical ureteroceles are mostly combined with a single kidney system and account for about 15% of cases. It is diagnosed more in older children or adults.

3.15.2.2 *Ectopic ureter*

The term ectopic ureter describes a ureter with the orifice located at the bladder neck, in the urethra, or outside the urinary tract. The ureter can drain the upper pole of a duplex or single system. There is a fundamental difference between the sexes. In boys, the ectopic orifice is never below the external sphincter.

In girls, the ureteral orifice may be located [759]:

- in the urethra, from the bladder neck to the meatus (35%);
- in the vaginal vestibule (34%);
- in the vagina (25%);
- in the uterus and Fallopian tube (6%).

In boys, the ureteral orifice may be located [759]:

- in the posterior urethra (47%);
- in the prostatic utricle (10%);
- in the seminal vesicles (33%);
- in the vas deferens or ejaculatory ducts (10%).

3.15.3 **Diagnostic evaluation**

3.15.3.1 *Ureterocele*

Prenatal US easily reveals voluminous obstructive ureteroceles [760, 761]. In cases with a small upper pole or a slightly obstructive ureterocele, prenatal diagnosis is difficult.

If prenatal diagnosis is impossible, the following clinical symptoms, besides incidental findings, can reveal the congenital anomaly at birth or later:

- At birth, a prolapsed and sometimes strangulated ureterocele may be observed in front of the urethral orifice. In a newborn boy, it might cause acute urinary retention, simulating urethral valves.
- The early symptom of pyelonephritis in either sex may lead to the diagnosis.
- Later symptoms can include dysuria, recurrent cystitis and urgency.

In cases of prenatal diagnosis, at birth, US confirms the ureteral dilatation that ends at the upper pole of a renal duplication. It also demonstrates the presence of a ureterocele in the bladder, with a dilated ureter behind the bladder.

At this point, it is important to assess the function of the upper pole using nuclear renography of the region of interest. This is best assessed with DMSA [762-764]. Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney, but cannot reliably predict histology [765]. Based on the prevalence of high-grade reflux, VCUG is mandatory for identifying ipsilateral or contralateral reflux, and assessing the degree of intra-urethral prolapse of the ureterocele [766]. Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic mega-ureter.

3.15.3.2 *Ectopic ureter*

Most of the ectopic mega-ureters are diagnosed primarily by US.

In some cases, clinical symptoms can lead to diagnosis:

- In neonates: dribbling of urine, pyuria, and acute pyelonephritis.
- In young girls: permanent urinary incontinence besides normal voiding, or significant vaginal discharge as the equivalent of incontinence; an ectopic orifice may be found in the meatal region [767].
- In pre-adolescent boys: epididymitis is the usual clinical presentation and the seminal vesicle may be palpable.

Ultrasound, radionuclide studies (DMSA, VCUG, MR urography, high-resolution MRI, and cystoscopy) are the diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction [768]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele [769, 770].

Girls who present with lifelong minimal urinary incontinence, never being dry, normal bladder function, complete emptying, and normal US are very suspicious for ectopic ureter. This needs to be excluded or confirmed by MRI as the most sensitive method [771]. Filling the bladder with methylene blue and checking for clear urine output from the vagina can give clear evidence of extra-sphincteric ureteral ectopia. This test is also helpful in confirming a vesicovaginal fistula (in this case blue fluid drains from the vagina).

3.15.4 **Management**

3.15.4.1 *Ureterocele*

Management is controversial with a choice between a non-operative approach, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, or complete primary reconstruction [772-777]. The choice of a therapeutic modality depends on the following criteria: clinical status of the patient (e.g. urosepsis); patient age; function of the upper pole; presence of reflux or obstruction of the ipsilateral or contralateral ureter; presence of bladder neck obstruction caused by ureterocele; intravesical or ectopic ureterocele; and parents' and surgeon's preferences [778]. When the diagnosis is made by US, prophylactic antibiotic treatment is indicated until a VCUG is performed.

3.15.4.1.1 Early treatment

In the presence of febrile infection or obstruction at the bladder neck, immediate endoscopic incision or puncture of the ureterocele is recommended. In a clinically asymptomatic child with a ureterocele and a non

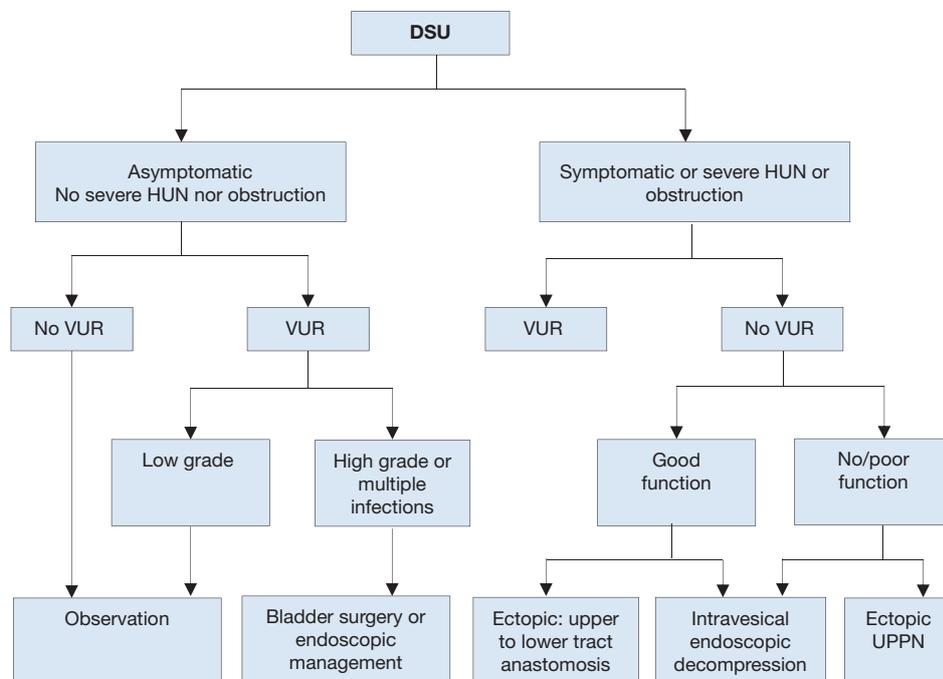
or hypofunctional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated.

3.15.4.1.2 Re-evaluation

Conservative treatment may be adopted in asymptomatic patients without any bladder outlet obstruction, severe hydronephrosis of the ureterocele moiety or high-grade (over grade III) reflux [778, 779]. If decompression is effective and there is no reflux (~25% of cases and more often in intravesical ureterocele), the patient is followed-up conservatively. After an endoscopic incision, most of the children with an extravesical ureterocele (50-80%) need a secondary procedure, compared with only 18% of those with an intravesical ureterocele [750]. Secondary surgery is necessary if decompression is not effective, significant reflux is present, or there is obstruction of the ipsi- or contralateral ureters, and/or bladder neck obstruction or retained ureterocele [780].

Surgery may vary from upper pole nephrectomy to complete unilateral LUT reconstruction [756, 776, 781-784]. In an ectopic ureterocele with severe hydronephrosis and without reflux, the primary upper tract approach without endoscopic decompression (partial upper-pole nephroureterectomy, pyelo/ureteropyelo/ureterostomy and upper-pole ureterectomy) has an 80% chance of being the definitive treatment [778, 785].

Figure 9: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life [778]



DSU = duplex system ureterocele; HUN = hydronephrosis; UPPN = upper pole partial nephrectomy; VUR = vesicoureteric reflux to the lower pole.

Obstruction is considered to be the presence of non-refluxing dilatation of non-ureterocele-bearing moieties (especially of the lower pole) or of an obstructive drainage pattern on diuretic renography.

3.15.4.2 Ectopic ureter

In the majority of cases, the upper pole is dysplastic and heminephro-ureterectomy should be considered. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) is a therapeutic option in cases in which the upper pole has function worth preserving. Both procedures can be performed through an open or laparoscopic approach [786-788]. In patients with bilateral single ectopic ureters (a very rare condition), an individual approach depending on the sex and renal and bladder function of the patient is necessary. Usually the bladder neck is insufficient in these patients [789-792].

3.15.5 Summary of evidence and recommendations for the management of obstructive pathology of renal duplication: ureterocele and ectopic ureter

Summary of evidence	LE
Ureterocele and ectopic ureter are associated with complete renal duplication, but they also occur in a single system.	1
In most cases, in young children (first years of life) diagnosis is done by US.	1
In older children clinical symptoms will prompt assessment.	1
Management includes a conservative approach, endoscopic decompression, partial nephroureterectomy, or complete primary reconstruction. Choice of treatment will depend on: <ul style="list-style-type: none"> clinical status of the patient (e.g., urosepsis); patient age; function of the upper pole; presence of reflux or obstruction of the ipsilateral or contralateral ureter; presence of bladder neck obstruction caused by ureterocele; intravesical or ectopic ureterocele; and parents' and surgeon's preferences. 	3

Recommendations		LE	GR	
Ureterocele	Diagnosis	Use ultrasound (US), radionuclide studies (mercaptoacetyltriglycine (MAG3)/dimercaptosuccinic acid (DMSA)), voiding cystourethrography (VCUG), magnetic resonance urography, high-resolution magnetic resonance imaging (MRI), and cystoscopy to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	3	B
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, complete primary reconstruction.	3	B
		Offer conservative treatment to patients (single/duplex systems) with no hydronephrosis and no symptoms, the risk for renal injury is low and conservative treatment is a good option.		
		Offer endoscopic treatment to patients with reflux; open re-implantation especially in dilating reflux provides better results.		
		Offer, early endoscopic decompression to patients with an obstructing ureterocele. In half to two-thirds of children with an extravesical ureterocele a secondary procedure is needed (compared to 20-25% of those with an intravesical ureterocele).		
		Offer heminephrectomy to patients with a non-functioning moiety and symptoms.		
Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	3	B
	Treatment	Select the most appropriate treatment option based on the function of the upper urinary tract.	3	B
		Offer (hemi-)nephroureterectomy in poorly or non-functioning moieties.		
	Offer ureteral re-implantation, ureteroureterostomy or ureteropyelostomy to patients with a functioning renal moiety, especially in cases in which the upper pole has function worth preserving.			

3.16 Disorders of sex development

3.16.1 Epidemiology, aetiology and pathophysiology

The formerly called 'intersex disorders' were recently the subject of a consensus document in which it was decided that the term 'intersex' should be changed to 'disorders of sex development' (DSD) [793, 794].

The new classification has arisen because of advances in knowledge of the molecular genetic causes of abnormal sexual development, controversies inherent to clinical management and ethical issues. Controversial and negative terminology, e.g. 'pseudohermaphroditism' and 'hermaphroditism', have been renamed according to the new pathophysiological insights. Furthermore, some conditions presenting with

severe male genital malformation, such as penile agenesis and cloacal exstrophy, which could not be categorised, have also been included. The term 'disorders of sex development' is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex. This will also include the idiopathic micropenis which is addressed here as a separate heading.

We refer to the consensus document as a general guideline, while this chapter will focus on what is relevant for the practising paediatric urologist. As the urologist is likely to be involved in both surgical and non-surgical neonatal work, this chapter will discuss the neonatal emergency and the diagnostic and therapeutic role of the paediatric urologist.

Overall, there is a low evidence base in the published literature on DSD. There are no RCTs and most studies are based on retrospective clinical descriptive studies (LE: 4) or on expert opinion. An exception is the risk of gonadal cancer, for which the LE is higher.

Disorders of sex development can present as prenatal diagnosis, neonatal diagnosis and late diagnosis. Prenatal diagnosis can be based on karyotype or US findings, neonatal diagnosis is based on genital ambiguity and late diagnosis is made on early or delayed puberty. In this guideline focus is on the neonatal presentation where the paediatric urologist plays a major role. For late diagnosis we refer to endocrinology and gynaecology guidelines on precocious and delayed puberty where paediatric urologists play a minor role [795, 796].

The diagnosis and treatment of DSD requires a multi-disciplinary approach, which should include geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers. Each team member should be specialised in DSD and a team should have enough patients to ensure experience.

3.16.1.1 *Micropenis*

Micropenis is a small but otherwise normally formed penis with a stretched length of < 2.5 SD below the mean [793, 794, 797].

Besides an idiopathic micropenis, two major causes of abnormal hormonal stimulation have been identified:

- hypogonadotropic hypogonadism (due to an inadequate secretion of GnRH);
- hypergonadotropic hypogonadism (due to failure of the testes to produce testosterone).

The penis is measured on the dorsal aspect, while stretching the penis, from the pubic symphysis to the tip of the glans [793]. The corpora cavernosa are palpated, the scrotum is often small, and the testes may be small and descended. Micropenis should be distinguished from buried and webbed penis, which is usually of normal size. The initial evaluation has to define whether the aetiology of the micropenis is central (hypothalamic/pituitary) or testicular. A paediatric endocrinology work-up has to be carried out immediately. Karyotyping is mandatory in all patients with a micropenis. Endocrine testicular function is assessed (baseline and stimulated testosterone, LH and FSH serum levels). Stimulated hormone levels may also give an idea of the growth potential of the penis. In patients with non-palpable testes and hypogonadotropic hypogonadism, laparoscopy should be carried out to confirm vanishing testes syndrome or intra-abdominal undescended hypoplastic testes. This investigation can be delayed until the age of one year [794].

Pituitary or testicular insufficiency are treated by the paediatric endocrinologist. In patients with testicular failure and proven androgen sensitivity, androgen therapy is recommended during childhood and at puberty to stimulate the growth of the penis [798-801] (LE: 2). In the presence of androgen insensitivity, good outcome of sexual function is questioned and gender conversion can be considered [802-804].

3.16.2 **Diagnostic evaluation**

3.16.2.1 *The neonatal emergency*

The first step is to recognise the possibility of DSD (Table 10) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. At the paediatric centre, the situation should be explained to the parents fully and kindly. Registering and naming the newborn should be delayed as long as necessary.

3.16.2.1.1 Family history and clinical examination

A careful family history must be taken followed by a thorough clinical examination (Table 11).

Table 10: Findings in a newborn suggesting the possibility of DSD (adapted from the American Academy of Pediatrics)

Apparent male
Severe hypospadias associated with bifid scrotum
Undescended testis/testes with hypospadias
Bilateral non-palpable testes in a full-term apparently male infant
Apparent female
Clitoral hypertrophy of any degree, non-palpable gonads
Vulva with single opening
Indeterminate
Ambiguous genitalia

Table 11: Diagnostic work-up of neonates with disorders of sex development

History (family, maternal, neonatal)
Parental consanguinity
Previous DSD or genital anomalies
Previous neonatal deaths
Primary amenorrhoea or infertility in other family members
Maternal exposure to androgens
Failure to thrive, vomiting, diarrhoea of the neonate
Physical examination
Pigmentation of genital and areolar area
Hypospadias or urogenital sinus
Size of phallus
Palpable and/or symmetrical gonads
Blood pressure
Investigations
Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH
Urine: adrenal steroids
Karyotype
Ultrasound
Genitogram
hCG stimulation test
Androgen-binding studies
Endoscopy

*ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone;
hCG = human chorionic gonadotropin; LH = luteinising hormone; TST = testosterone.*

3.16.2.1.2 Choice of laboratory investigations

The following laboratory investigations are mandatory:

- karyotype;
- plasma 17-hydroxyprogesterone assay;
- plasma electrolytes;
- ultrasound to evaluate the presence of Müllerian duct structures.

These investigations will provide evidence of congenital adrenal hyperplasia (CAH), which is the most frequently occurring DSD. If this evidence is found, no further investigation is needed. If not, then the laboratory work-up should proceed further.

The hCG stimulation test is particularly helpful in differentiating the main syndromes of 46XYDSD by evaluating Leydig cell potential. When testosterone metabolism is evaluated, the presence or absence of metabolites will help to define the problem. An extended stimulation can help to define phallic growth potential and to induce testicular descent in some cases of associated cryptorchidism.

3.16.2.2 Gender assignment

This is a very complicated task. It should take place after a definitive diagnosis has been made.

The idea that an individual is sex-neutral at birth and that rearing determines gender development is no longer the standard approach. Instead, gender assignment decisions should be based upon:

- age at presentation;
- fertility potential;
- size of the penis;
- presence of a functional vagina;
- endocrine function;
- malignancy potential;
- antenatal testosterone exposure;
- general appearance;
- psychosocial well-being and a stable gender identity;
- sociocultural aspect;
- parental opinions.

Each patient presenting with DSD should be assigned a gender as quickly as a thorough diagnostic evaluation permits. Minimal time needed is 48 hours. During this period any referral to gender should be avoided, better to address the patient as “the child”, “your child”.

3.16.2.3 Role of the paediatric urologist

The role of the paediatric urologist can be divided into a diagnostic role and a therapeutic role (Table 12). Each of these roles will be discussed briefly.

Table 12: Role of the paediatric urologist

Diagnostic role
<ul style="list-style-type: none"> • Clinical examination • Ultrasound • Genitography • Cystoscopy • Diagnostic laparoscopy
Therapeutic role
<ul style="list-style-type: none"> • Masculinising surgery • Feminising surgery • Gonadectomy

3.16.2.3.1 Clinical examination

A thorough clinical examination in a neonate presenting with ambiguous genitalia is important. As well as a accurate description of the ambiguous genitalia, detailed information should be given on palpability and localisation of the gonads. Information gathered by the various examinations described below should help the team to come to a final diagnosis.

Palpable gonad. If it is possible to feel a gonad, it is almost certainly a testis; this clinical finding therefore virtually excludes 46XXDSD.

Medical photography can be useful but requires sensitivity and consent [805].

Phallus. The phallus should be measured. A cotton bud placed at the suprapubic base of the implant of the stretched phallus allows for a good measurement of phallic length.

Urogenital sinus opening. The opening of the urogenital sinus must be well evaluated. Is there only one opening visible? Can a hymenal ring be seen? What does the fusion of the labioscrotal folds look like; do the folds show rugae or some discolouration?

3.16.2.3.2 Investigations

Ultrasound can help to describe the palpated gonads or to detect non-palpable gonads. However, the sensitivity and specificity are not high. On US, the Müllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utricular structure visible [806, 807]?

Genitography can provide some more information on the urogenital sinus. How low or how high is the confluence? Is there any duplication of the vagina? How does the urethra relate to the vagina?

General anaesthesia. In some cases, further examinations under general anaesthesia can be helpful. On cystoscopy, the urogenital sinus can be evaluated and the level of confluence between the bladder neck and the bladder. Cystoscopy can also be used to evaluate the vagina or utriculus, e.g. the presence of a cervix at the top of the vagina can be important information.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed [808, 809].

3.16.3 **Management**

Referring to the consensus document [793, 794], it is clear that the timing of surgery is much more controversial than it used to be. The rationale for early surgery includes:

- beneficial effects of oestrogen on infant tissue;
- avoiding complications from anatomical anomalies;
- minimising family distress;
- mitigating the risks of stigmatisation and gender-identity confusion [810].

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Early surgery should be reserved for those patients with high confluent urogenital tracts, girls with severely masculinised genitalia and boys with undervirilised genitals. Vaginoplasty should be delayed until puberty and milder forms of masculinisation should not be treated surgically. Recently the ESPU and SPU have taken a position in the debate on surgery for DSD [811].

3.16.3.1 *Feminising surgery*

Clitororeduction. Reduction of an enlarged clitoris should be done with preservation of the neurovascular bundle. Clitoral surgery has been reported to have an adverse outcome on sexual function and should therefore be limited to severely enlarged clitorises [812, 813]. Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown [814].

Separation of the vagina and the urethra is preserved for high confluence anomalies. Many techniques for urogenital sinus repair have been described, but their outcome has not been evaluated prospectively [815, 816].

Vaginoplasty should be performed during the teenage years. Every technique (self-dilatation, skin or bowel substitution) has its specific advantages and disadvantages [817]. All carry a potential for scarring that would require further surgery before sexual function was possible.

Aesthetic refinements. The goals of genital surgery are to maximise anatomy to allow sexual function and romantic partnering. Aesthetics are important in this perspective. The reconstruction of minor labiae from an enlarged clitoral hood is an example of aesthetic refinement.

3.16.3.2 *Masculinising surgery*

Hormone therapy early in life is advocated by many doctors. The level of evidence is low for restoration of normal penile size.

Hypospadias surgery. See section on hypospadias (Chapter 3.5).

Excision of Mullerian structures. In the DSD patient assigned a male gender, Müllerian structures should be excised. There is no evidence on whether utricular cysts need to be excised.

Orchiopexy. See section on orchiopexy (Chapter 3.2).

Phalloplasty. Increasing experience of phalloplasty in the treatment of female to male transsexual patients has led to reports about the reliability and feasibility of this technique. It has therefore become available to treat severe penile inadequacy in DSD patients.

Aesthetic refinements. These include correction of penoscrotal transposition, scrotoplasty and insertion of testicular prostheses.

Gonadectomy. Germ cell malignancy only occurs in patients with DSD who have Y-chromosomal material. The highest risk is seen in patients with gonadal dysgenesis and in patients with partial androgen insensitivity with intra-abdominal gonads (LE: 2). Intra-abdominal gonads of high-risk patients should be removed at the time of diagnosis [818].

3.16.4 **Summary of evidence and recommendations for the management of disorders of sex development**

Summary of evidence	LE
Timing of surgery will be dependent on the severity of the condition and on the assigned sex.	4
In boys the surgical correction will mainly consist of hypospadias repair and orchiopexy, so the timing will follow the recommendations for hypospadias repair and orchiopexy (from six months onwards and before two years of age).	2

Recommendations	GR
Treat disorders of sex development (DSD) within a multi-disciplinary team.	A
Refer children to experienced centres where neonatology, paediatric endocrinology, paediatric urology, child psychology and transition to adult care are guaranteed.	A
Do not delay treatment of any neonate presenting with ambiguous genitalia since salt-loss in a 46XX CAH girl can be fatal.	A
Gender assignment is imminent and should be based on multi-disciplinary consensus taking into account the latest knowledge.	B
Do not delay surgical treatment in girls presenting with severe anomalies.	B
Offer more conservative approaches in less severe cases, in consultation with the parents.	B
Follow the recommendations for boys, for hypospadias repair and orchiopexy (from six months onwards and before two years of age).	A

3.17 **Posterior urethral valves**

3.17.1 **Epidemiology, aetiology and pathophysiology**

Posterior urethral valves (PUV) are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. Despite optimal treatment, PUV in children may result in renal insufficiency in nearly one-third of cases [819-821]. Posterior urethral valves are found in 1 in 1,250 in a population undergoing foetal US screening [519]. An incidence of PUV of 1 in 5,000-12,500 live-births has been estimated [822, 823]. In one report, up to 46% of foetuses with a PUV diagnosis were terminated, indicating a possible decrease in incidence [824].

3.17.2 **Classification systems**

3.17.2.1 **Urethral valve**

Despite recent attempts to introduce new classification terms, such as 'congenital obstructive posterior urethral membrane' (COPUM) [825], the original classification by Hugh Hampton Young remains the most commonly used [826].

Hugh Hampton Young described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. As type II seems to be more like a fold and not obstructive, it is no longer referred to as a valve. Hampton Young's descriptions of type I and III are as follows:

Type I (90-95%). 'In the most common type there is a ridge lying on the floor of the urethra, continuous with the verumontanum, which takes an anterior course and divides into two fork-like processes in the region of the bulbo-membranous junction. These processes are continued as thin membranous sheets, direct upward and forward which may be attached to the urethra throughout its entire circumference. It is generally supposed that the valves have complete fusion anteriorly, leaving only an open channel at the posterior urethral wall. Yet, the fusion of the valves anteriorly may not be complete in all cases, and at this point a slight separation of the folds exists' [826].

Type III. 'There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum. This obstruction was attached to the entire circumference of the urethra, with a small opening in the centre' [826]. The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane [827]. The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca [828].

3.17.3 *Diagnostic evaluation*

An obstruction above the level of the urethra affects the whole urinary tract to varying degrees.

- The prostatic urethra is distended and the ejaculatory ducts may be dilated due to urinary reflux.
- The bladder neck is hypertrophied and rigid.
- The hypertrophied bladder occasionally has multiple diverticula.
- Nearly all valve patients have dilatation of both UUT. This may be due to the valve itself and the high pressure in the bladder, or due to obstruction of the ureterovesical junction by the hypertrophied bladder.
- If there is secondary reflux, the affected kidney functions poorly in most cases.

During prenatal US screening, bilateral hydronephrosis and a distended bladder are suspicious signs of a urethral valve. Also a thick-walled bladder and a dilated posterior urethra ('keyhole' sign) make a PUV likely. In one study, however, the keyhole sign was not found to be a reliable predictor ($p = 0.27$) [829]. In the presence of increased echogenicity of the kidney, dilatation of the urinary tract and oligohydramnion, the diagnosis of a PUV should strongly be considered.

Voiding cystourethrogram confirms a PUV diagnosis. This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well outlined during voiding. A secondary reflux is observed in at least 50% of patients with PUV [830]. Reflux is consistently associated with renal dysplasia in patients with PUV. It is generally accepted that reflux in the renal units acts as a 'pressure pop-off valve', which would protect the other kidney, leading to a better prognosis [831]. Other types of pop-off mechanism include bladder diverticula and urinary extravasation, with or without urinary ascites [832]. However, in the long-term, a supposed protective effect did not show a significant difference compared to other patients with PUV [833, 834].

Nuclear renography with split renal function is important to assess kidney function (DMSA or MAG3). Creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. A nadir creatinine of 80 $\mu\text{mol/L}$ is correlated with a better prognosis [821]. Initial management includes a multi-disciplinary team involving a paediatric nephrologist.

3.17.4 **Management**

3.17.4.1 *Antenatal treatment*

About 40-60% of PUV are discovered before birth [835]. The intrauterine obstruction leads to a decreased urine output, which could result in an oligohydramnios. Amniotic fluid is necessary for normal development of the lung and its absence may lead to pulmonary hypoplasia, causing a life-threatening problem. Intrauterine attempts have been made to treat a foetus with PUV.

As renal dysplasia is not reversible, it is important to identify those foetuses with good renal function. A sodium level below 100 mmol/L, a chloride value of $< 90\text{mmol/L}$ and an osmolarity below 200 mOsm/L found in three foetal urine samples gained on three different days are associated with a better prognosis [836].

The placing of a vesicoamniotic shunt has a complication rate of 21-59%, dislocation of the shunt occurs in up to 44%, mortality lies between 33% and 43%, and renal insufficiency is above 50% [836-838]. Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and longterm results of patients with PUV [837, 838]. The PLUTO-trial (randomised study) could not prove a benefit of placing a shunt [839].

Foetal valve treatment e.g laser ablation has a high complication rate without evidence for the effectiveness of these interventions. Therefore this should be still considered as an experimental intervention [840, 841].

3.17.4.2 *Postnatal treatment*

Bladder drainage. If a boy is born with suspected PUV, drainage of the bladder and, if possible, an immediate VCUG is necessary. A neonate can be catheterised with a 3.5-5 F catheter. Balloon catheters are not available in this size. A VCUG is performed to see if the diagnosis is correct and whether the catheter is within the bladder and not in the posterior urethra. An alternative option is to place a suprapubic catheter, perform a VCUG and leave the tube until the neonate is stable enough to perform an endoscopic incision or resection of the valve.

Valve ablation. When the medical situation of the neonate has stabilised and the creatinine level decreased, the next step is to remove the intravesical obstruction. In cases where the urethra is too small to safely pass a small faetal cystoscope, a suprapubic diversion is performed until valve ablation can be performed. Small paediatric cystoscopes and resectoscopes are now available either to incise, ablate or to resect the valve at the 4-5, 7-8 or 12 o'clock position, or at all three positions, depending on the surgeon's preference. It is important to avoid

extensive electrocoagulation, as the most common complication of this procedure is stricture formation. One recently published study demonstrated a significant lower urethral stricture rate using the cold knife compared to diathermy [842]. Within the three months following initial treatment, a control VCUG or a re-look cystoscopy should demonstrate the effectiveness of the treatment, depending on the clinical course [843].

Vesicostomy. If the child is too small and/or too ill to undergo endoscopic surgery, a suprapubic diversion is performed to drain the bladder temporarily. If initially a suprapubic tube has been inserted, this can be left in place for six to twelve weeks. Otherwise, a cutaneous vesicostomy provides an improvement or stabilisation of the UUT in over 90% of cases [844]. Although there has been concern that a vesicostomy could decrease bladder compliance or capacity, so far there are no valid data to support these expectations [845, 846].

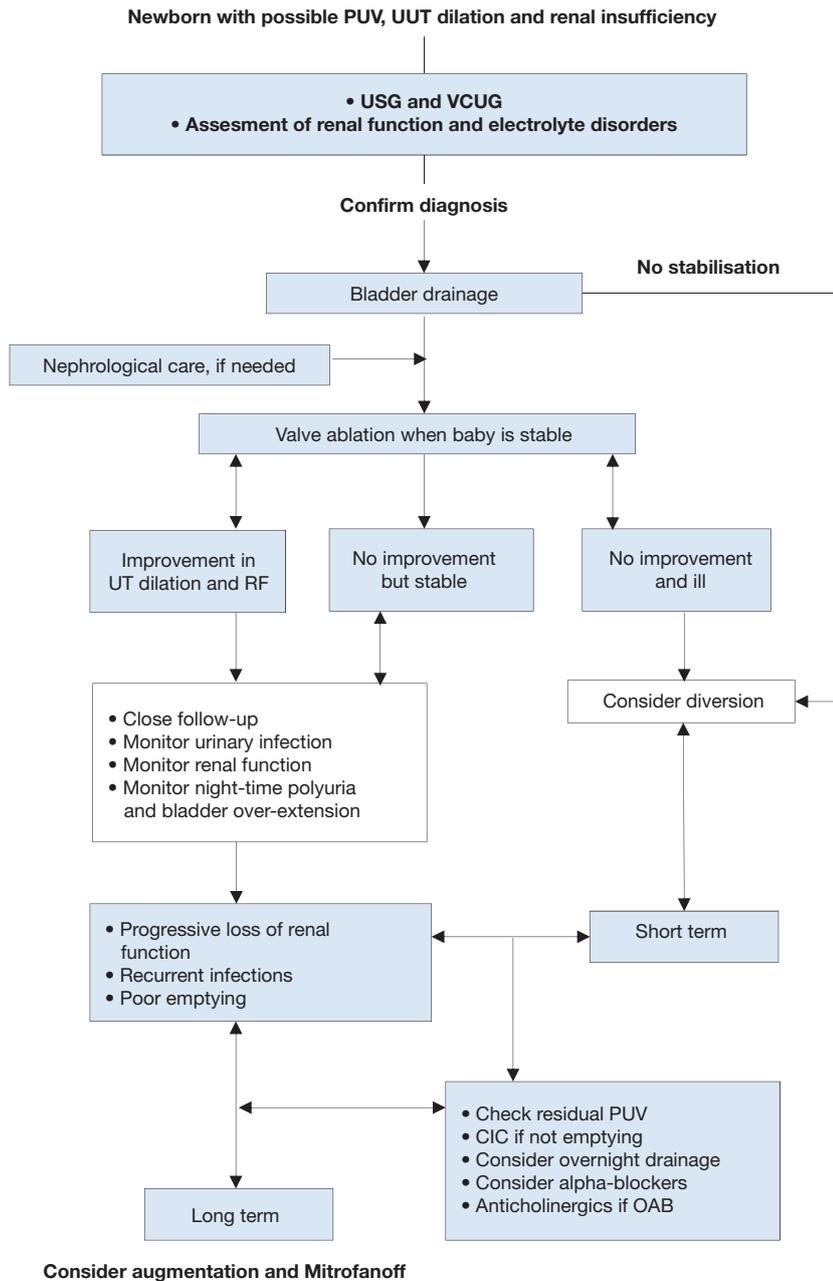
High diversion. If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. The choice of urinary diversion depends on the surgeon's preference for high loop ureterostomy, ring ureterostomy, end ureterostomy or pyelostomy, with each technique having advantages and disadvantages [847-849]. Reconstructive surgery should be delayed until the UUT has improved as much as can be expected.

Reflux is very common in PUV patients (up to 72%) and it is described bilaterally in up to 32% [850]. During the first months of life, antibiotic prophylaxis may be given especially in those with high-grade reflux [600] and in those with a phimosis, circumcision can be discussed in order to reduce the risk of UTIs [851]. However, there are no randomised studies to support this for patients with PUV. High-grade reflux is associated with a poor functioning kidney and is considered a poor prognostic factor [819, 852]. However, early removal of the renal unit seems to be unnecessary, as long as it causes no problems. It may be necessary to augment the bladder and in this case the ureter may be used [853].

3.17.5 **Follow-up**

Life-long monitoring of these patients is mandatory, as bladder dysfunction ('valve bladder') is not uncommon and the delay in day- and night-time continence is a major problem [821, 830]. Poor bladder sensation and compliance, detrusor instability and polyuria (especially at night) and their combination are responsible for bladder dysfunction. In those with bladder instability, anticholinergic therapy can improve bladder function. However, with a low risk of reversible myogenic failure (3/37 patients in one study) [854, 855]. In patients with poor bladder emptying α -blocker can be used to reduce the PVR urine, as demonstrated in one study with 42 patients using terazosin (mean PVR) was reduced from 16 to 2 mL [856] and in another study tamsulosin was effective [857]. Between 10% and 47% of patients may develop end-stage renal failure [819-821]. High creatinine nadir and severe bladder dysfunction are risk factors for renal replacement therapy [858]. Renal transplantation in these patients can be performed safely and effectively [859, 860]. Deterioration of the graft function is mainly related to LUTD [860, 861]. An assessment and treatment algorithm is provided in Figure 10.

Figure 10: An algorithm on the assessment, management and follow-up of newborns with possible PUV



CIC = clean intermittent catheterisation; OAB = overactive bladder; PUV = posterior urethral valve; RF = renal function; UT = urinary tract; UUT = upper urinary tract; VCUG = voiding cystourethrogram.

3.17.6 Summary

Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period and despite optimal treatment result in renal insufficiency in nearly one-third of cases. Bilateral hydronephrosis and a distended bladder are suspicious signs of a PUV in neonates. A VCUG confirms a PUV diagnosis. Nuclear renography with split renal function is important to assess kidney function and serum creatinine nadir above 80 $\mu\text{mol/L}$ is correlated with a poor prognosis.

Postnatal treatment includes bladder drainage either transurethral or suprapubic and if the child is stable enough, endoscopic incision of the valve is performed. If a child is too small and/or too ill to undergo endoscopic surgery, a vesicostomy is an option for bladder drainage. If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered.

In all patients life-long monitoring is mandatory, as bladder dysfunction is quite common and may cause progressive upper tract deterioration, if not managed properly. In the long run between 10% and 47% of patients may develop end-stage renal failure. Renal transplantation in these patients can be performed safely and effectively.

3.17.7 **Summary of evidence and recommendations for the management of posterior urethral valves**

Summary of evidence	LE
Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period.	1b
Despite optimal treatment nearly one-third of the patients end up in renal insufficiency.	2b
Bilateral hydroureteronephrosis and a distended bladder are suspicious signs on US; a VCUG confirms the diagnosis.	2b
Serum creatinine nadir above 80 µmol/L is correlated with a poor prognosis.	2a
In the long run between 10% and 47% of patients develop end-stage renal failure due to primary dysplasia and/or further deterioration because of bladder dysfunction.	2a
Renal transplantation in these patients is safe and effective, if the bladder function is normalised.	

Recommendations	LE	GR
Diagnose posterior urethral valves (PUV) initially by ultrasound (US) but a voiding cystourethrogram (VCUG) is required to confirm the diagnosis. Assess split renal function by dimercaptosuccinic acid (DMSA) scan or mercaptoacetyltriglycine (MAG3) clearance. Serum creatinine is the prognostic marker.	3	B
Vesico-amniotic shunt antenatally is not recommended to improve renal outcome.	1b	A
Offer endoscopic valve ablation after bladder drainage and stabilisation of the child.	3	B
Offer suprapubic diversion for bladder drainage if the child is too small for urethral surgery.		
Offer a high urinary diversion if bladder drainage is insufficient to drain the UUT and the child remains unstable.		
Monitor bladder- and renal function lifelong, in all patients.	3	B

3.18 **Paediatric urological trauma**

Trauma is the leading cause of morbidity and mortality in children and is responsible for more childhood deaths than the total of all other causes [862]. In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract [863]. This is caused by either blunt injuries from falls, car accidents, sports injuries, physical assault, and sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

3.18.1 **Paediatric renal trauma**3.18.1.1 *Epidemiology, aetiology and pathophysiology*

In blunt abdominal trauma, the kidney is the most commonly affected organ, accounting for about 10% of all blunt abdominal injuries [862].

Children are more likely than adults to sustain renal injuries after blunt trauma because of their anatomy. Compared to an adult kidney, a child's kidney is larger in relation to the rest of the body and often retains foetal lobulations, so that blunt trauma is more likely to lead to a local parenchymal disruption. The paediatric kidney is also less well protected than the adult kidney. Children have less peri-renal fat, much weaker abdominal muscles, and a less ossified and therefore much more elastic and compressible thoracic cage [864].

Blunt renal trauma is usually a result of sudden deceleration of the child's body, particularly due to sport accidents, falls, and contact with blunt objects. Deceleration or crush injuries result in contusion, laceration or avulsion of the less well-protected paediatric renal parenchyma.

3.18.1.2 *Classification systems*

Renal injuries are classified according to the kidney injury scale of the American Association for the Surgery of Trauma (Table 13) [865].

Table 13: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [865]

Grade	Type of injury	Description
I	Contusion	Non-visible or visible haematuria
	Haematoma	Normal urological studies
II	Haematoma	Non-expanding subcapsular haematoma
	Laceration	Laceration of the cortex of < 1.0 cm
III	Laceration	Laceration > 1.0 cm without rupture of collecting system
IV	Laceration	Through the cortex, medulla and collecting system
	Vascular	Vascular injury
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of the renal hilum

3.18.1.3 Diagnostic evaluation

In a child who has sustained blunt abdominal trauma, renal involvement can often be predicted from the history, physical examination and laboratory evaluation. Renal involvement may be associated with abdominal or flank tenderness, lower rib fractures, fractures or vertebral pedicles, trunk contusions and abrasions, and haematuria.

3.18.1.3.1 Haematuria

Haematuria may be a reliable finding. In severe renal injuries, 65% suffer visible haematuria and 33% non-visible, while only 2% have no haematuria at all [866].

The radiographic evaluation of children with suspected renal trauma remains controversial. Some centres rely on the presence of haematuria to diagnose renal trauma, with a threshold for renal involvement of 50 RBCs/HPF. Although this may be a reliable threshold for significant non-visible in trauma, there have been many reports of significant renal injuries that manifest with little or even no blood in the urine [867]. It is therefore compulsory to consider all the clinical aspects involved, including the history, physical examination, consciousness of the child, overall clinical status and laboratory findings to decide on the diagnostic algorithm and whether or not a child needs further imaging studies.

3.18.1.3.2 Blood pressure

It is important to consider that children, unlike adults, are able to maintain their blood pressure, even in the presence of hypovolaemia, due to compliance of the vascular tree and mechanisms for cardiac compensation [868]. Because blood pressure is an unreliable predictor of renal involvement in children, some centres recommend imaging of the urinary tract in children with any degree of haematuria following significant abdominal trauma.

3.18.1.3.3 Choice of imaging method

Nowadays, CT is the best imaging method for renal involvement in children. Computed tomography scanning is the cornerstone of modern staging of blunt renal injuries especially when it comes to grading the severity of renal trauma

Computed tomography scanning is quite rapid and usually performed with the injection of contrast media. To detect extravasation, a second series of images is necessary since the initial series usually finishes 60 seconds after injection of the contrast material and may therefore fail to detect urinary extravasation [869]. In acute trauma, US may be used as a screening tool and for reliably following the course of renal injury. However, US is of limited value in the initial and acute evaluation of trauma. The Standard Intravenous Pyelogram is a good alternative imaging method if a CT scan is not available. It is superior to US but not as good as CT scanning for diagnostic purposes.

3.18.1.4 Disease management

The modern management of trauma is multidisciplinary, requiring paediatricians, emergency physicians, surgeons, urologists, and other specialties as required.

Non-surgical conservative management with bed rest, fluids and monitoring has become the standard approach for treating blunt renal trauma. Even in high-grade renal injuries, a conservative approach is effective and recommended for stable children. However, this approach requires close clinical observation, serial CT scans, and frequent re-assessment of the patient's overall condition.

Absolute indications for surgery include persistent bleeding into an expanding or unconfined haematoma. Relative indications for surgery are massive urinary extravasation and extensive non-viable renal tissue [870].

3.18.1.5 *Recommendations for the diagnosis and management of paediatric renal trauma*

Recommendations	GR
Use imaging in all children who have sustained a blunt or penetrating trauma with any level of haematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.	B
Use rapid spiral computed tomography scanning for diagnostic and staging purposes.	B
Manage most injured kidneys conservatively.	B
Offer surgical intervention in case of haemodynamic instability and a Grade V renal injury.	A

3.18.2 **Paediatric ureteral trauma**

Injuries to the ureter are rare. The ureter is well protected; the upper part is protected by its close approximation to the vertebral column and paraspinal muscles and the lower part by its route through the bony pelvis. In addition, the ureter is a small target, and both flexible and mobile. This also means that ureteral injuries are caused more often by penetrating trauma than blunt trauma [871]. Since the ureter is the sole conduit for urinary transport between the kidney and the bladder, any ureteral injury can threaten the function of the ipsilateral kidney.

3.18.2.1 *Diagnostic evaluation*

Since there are no classical clinical symptoms suggestive of ureteral trauma, it is important to carry out a careful diagnostic work-up using different imaging modalities. Unfortunately, initial imaging studies, such as IVP and routine CT scans, are unreliable; a study of eleven disruptions of the ureteropelvic junction found that 72% had a normal or non-diagnostic IVP on initial studies [871]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to ten minutes after injection of the contrast material [872]. The most sensitive diagnostic test is a retrograde pyelogram.

Quite a few patients present several days after the injury, when the urinoma produces flank and abdominal pain, nausea and fever.

Because the symptoms may often be quite vague, it is important to remain suspicious of a potential undiagnosed urinary injury following significant blunt abdominal trauma in a child.

3.18.2.2 *Management*

Immediate repair during abdominal exploration is rare. Minimally invasive procedures are the method of choice, especially since many ureteral injuries are diagnosed late after the traumatic event. Percutaneous or nephrostomy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries [873].

If endoscopic management is not possible, primary repair of partial lacerations should be followed by internal stenting. The management of complete lacerations, avulsions or crush injuries depends on the amount of ureter lost and its location. If there is an adequate healthy length of ureter, a primary ureteroureterostomy can be performed. If primary re-anastomosis is not achievable, distal ureteral injuries can be managed using a psoas bladder hitch, Boari flap or even nephropexy. Proximal injuries can be managed using transureteroureterostomy, autotransplantation or ureteral replacement with bowel or appendix [874].

3.18.2.3 *Recommendations for the diagnosis and management of paediatric ureteral trauma*

Recommendations	GR
Diagnose suspected ureteral injuries by retrograde pyelogram.	
However, in the initial phase of an injury, it is very likely that ureteral injuries will not be detected by routine imaging methods, including contrast-enhanced spiral computed tomography.	A
Manage ureteral injuries endoscopically, using internal stenting or drainage of a urinoma, either percutaneously or via a nephrostomy tube.	B
Manage distal and proximal ureteral injuries with open surgery.	B
Manage distal injuries with direct re-anastomosis and ureteroneocystostomy.	B
Manage proximal injuries, with transureteroureterostomy, ureteral replacement with bowel or appendix, or even autotransplantation.	B

3.18.3 **Paediatric bladder injuries**

The paediatric bladder is less protected than the adult bladder, and is therefore more susceptible to injuries than the adult bladder, especially when it is full, due to:

- Its higher position in the abdomen and its exposure above the bony pelvis.
- The fact that the abdominal wall provides less muscular protection.
- The fact that there is less pelvic and abdominal fat surrounding the bladder to cushion it in trauma.

Blunt trauma is the most common cause of significant bladder injury. In adults, bladder injury is often associated with pelvic fractures. This is less common in children because the paediatric bladder sits above the pelvic ring. In a large prospective study, only 57% of children with pelvic fractures also had a bladder injury compared to 89% of adults [875].

3.18.3.1 Diagnostic evaluation

The characteristic signs of bladder injury are suprapubic pain and tenderness, an inability to urinate, and visible haematuria (95% of injuries). Patients with a pelvic fracture and visible haematuria present with a bladder rupture in up to 45% of cases [876].

The diagnosis of bladder rupture can be difficult in some cases. The bladder should be imaged both when fully distended and after drainage using standard radiography or a CT scan. The best results can be achieved by retrograde filling of the bladder using a catheter. Despite advances in CT imaging, the bladder must still be filled to capacity to accurately diagnose a possible bladder injury [877].

Blunt injuries to the bladder are categorised as:

- contusions with damage to the bladder mucosa or muscle, without loss of bladder wall continuity or extravasation;
- ruptures, which are either intraperitoneal or extraperitoneal.

Intra-peritoneal bladder ruptures are more common in children because of the bladder's exposed position and the acute increase in pressure during trauma. These cause the bladder to burst at its weakest point, i.e. the dome. Extraperitoneal lesions occur in the lower half of the bladder and are almost always associated with pelvic fractures. A cystogram will show extravasation into the perivesical soft tissue in a typical flame pattern and the contrast material is confined to the pelvis.

3.18.3.2 Management

Contusions usually present with varying degrees of haematuria and are treated with catheter drainage alone.

3.18.3.2.1 Intra-peritoneal injuries

The accepted management of intra-peritoneal bladder ruptures is open surgical exploration and primary repair. Post-operative drainage with a suprapubic tube is mandatory. Recent data suggest that transurethral drainage may be as effective, with fewer complications, resulting in shorter periods of diversion [878]. Usually, after about seven to ten days, a repeat cystogram is performed to ensure healing is taking place properly.

3.18.3.2.2 Extra-peritoneal injuries

Non-operative management with catheter drainage for seven to ten days alone is the method of choice for extra-peritoneal bladder rupture. However, if there are bone fragments within the bladder, these must be removed and the bladder must then be repaired and drained, according to the principles for treating intraperitoneal ruptures [879].

3.18.3.3 Recommendations for the diagnosis and management of paediatric bladder injuries

Recommendations	GR
Use retrograde cystography to diagnose suspected bladder injuries.	
Ensure that the bladder has been filled to its full capacity and an additional film is taken after drainage.	A
Manage extra-peritoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	A
Do not delay treatment of intra-peritoneal bladder ruptures by surgical exploration and repair as well as post-operative drainage for seven to ten days.	A

3.18.4 Paediatric urethral injuries

Except for the penile part of the urethra, the paediatric urethra is quite well protected. In addition, its shape and elasticity mean the urethra is seldom injured by trauma. However, a urethral injury should be suspected in any patient with a pelvic fracture or significant trauma to the perineum until confirmed otherwise by a diagnostic work-up.

3.18.4.1 Diagnostic evaluation

Patients with suspected urethral trauma and pelvic fractures usually present with a history of severe trauma, often involving other organ systems.

Signs of urethral injury are blood at the meatus, visible haematuria, and pain during voiding or an inability to void. There may also be perineal swelling and haematoma involving the scrotum. A rectal examination to determine the position and fixation of the prostate is important in any male with a suspected urethral injury. The prostate, as well as the bladder, may be displaced up out of the pelvis, especially in membranous urethral trauma.

Radiographic evaluation of the urethra requires a retrograde urethrogram. It is important to expose the entire urethral length, including the bladder neck. If a catheter has already been placed by someone else and there is suspected urethral trauma, the catheter should be left in place and should not be removed. Instead, a small infant feeding tube can be placed into the distal urethra along the catheter to allow the injection of contrast material for a diagnostic scan [880].

3.18.4.2 Disease management

Since many of these patients are unstable, the urologist's initial responsibility is to provide a method of draining and monitoring urine output.

A transurethral catheter should only be inserted if there is a history of voiding after the traumatic event, and if a rectal and pelvic examination, as described above, has not suggested a urethral rupture. If the catheter does not pass easily, an immediate retrograde urethrogram should be performed.

A suprapubic tube may be placed in the emergency department percutaneously, or even in the operating room, if the patient has to undergo immediate exploration because of other life-threatening injuries.

There are often no associated injuries with a bulbous urethral or straddle injury and management is therefore usually straightforward. In these cases, a transurethral catheter is the best option for preventing urethral bleeding and/or painful voiding [881].

The initial management of posterior urethral injuries remains controversial, mainly regarding the long-term results with primary realignment compared to simple suprapubic drainage with later reconstruction.

The main goals in the surgical repair of posterior urethral injuries are:

- Providing a stricture-free urethra.
- Avoiding the complications of urinary incontinence and impotence.

Suprapubic drainage and late urethral reconstruction was first attempted because immediate surgical repair had a poor outcome, with significant bleeding and high rates of incontinence (21%) and impotence in up to 56% of cases [882]. In adults, a study of the success rates of delayed repair reported re-structure rates of 11-30%, continence rates of 90-95% and impotence rates of 62-68% [883]. However, in children, there is much less experience with delayed repair. The largest paediatric series of delayed repair in 68 boys reported a success rate of 90% [884]. Another study reported strictures and impotence in 67% of boys, although all the boys were continent [883].

An alternative to providing initial suprapubic drainage and delayed repair is primary realignment of the urethra via a catheter. The catheter is usually put in place during open cystostomy by passing it from either the bladder neck or meatus and through the injured segment. In a series of fourteen children undergoing this procedure, this resulted in a stricture rate of 29% and incontinence in 7% of patients [885].

3.18.4.3 Recommendations for the diagnosis and management of paediatric trauma

Recommendations	GR
Assess the urethra by retrograde urethrogram in case of suspected urethral trauma.	A
Perform a rectal examination to determine the position of the prostate.	B
Manage bulbous urethral injuries conservatively with a transurethral catheter.	B
Manage posterior urethral disruption by either: <ul style="list-style-type: none"> • primary reconstruction; • primary drainage with a suprapubic catheter alone and delayed repair; • primary re-alignment with a transurethral catheter. 	C

3.19 Post-operative fluid management

3.19.1 Epidemiology, aetiology and pathophysiology

Compared to adults, children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms [886]. As children are developing,

they have a high metabolic rate and low fat and nutrient stores, which means they are more susceptible to metabolic disturbances caused by surgical stress [887]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [888].

3.19.2 **Disease management**

3.19.2.1 *Pre-operative fasting*

Pre-operative fasting has been advocated for elective surgery to avoid the complications associated with pulmonary aspiration during induction of anaesthesia. Table 14 gives the current guidelines for pre-operative fasting for elective surgery [889, 890].

Table 14: Pre-operative fasting times for elective surgery

Ingested material	Minimum fasting period (hours)
Clear liquids	2
Breast milk	4
Infant formula	4 (< 3 months old) to 6 (> 3 months old)
Non-human milk	6
Light meal	6

Although hypoglycaemia is an important issue in children, research has shown that hypoglycaemia is uncommon if children are still fed up to four hours before the induction of anaesthesia [891]. Newborns often have low glycogen stores and impaired gluconeogenesis, both of which can be helped by limiting the period of pre-operative starvation and feeding with glucose-containing solutions. It is important to monitor blood glucose and to adjust the glucose supply continuously in neonates and children who are small for their age, as this helps to prevent excessive fluctuation in blood glucose levels [892].

3.19.2.2 *Maintenance therapy and intra-operative fluid therapy*

Generally, the anaesthetist is responsible for intra-operative management and the surgeon is responsible for post-operative instructions. The goal of intra-operative fluid management is to sustain homeostasis by providing the appropriate amount of parenteral fluid; this maintains adequate intravascular volume, cardiac output and oxygen delivery to tissues at a time when normal physiological functions have been altered by surgical stress and anaesthetic agents [892].

The fluids for maintenance therapy replace losses from two sources: insensible (evaporation) and urinary loss. They do not replace blood loss or third-space fluid loss into the interstitial space or gut. The main formulae for calculating the daily maintenance requirement for water have not changed in the past 50 years (Table 15) [893]. Calculations have shown that anaesthetised and non-anaesthetised children have similar fluid requirements [894].

The combination of maintenance fluid and electrolyte requirements results in a hypotonic electrolyte solution. The usual intravenous maintenance fluid given to children by paediatricians is one-quarter to one-third strength saline [895].

Table 15: Hourly and daily fluid requirements according to body weight

Body weight	Hourly	Daily
< 10 kg	4 mL/kg	100 mL/kg
10-20 kg	40 mL + 2 mL/kg; > 10 kg	1,000 mL + 50 mL/kg; > 10 kg
> 20 kg	60 mL + 1 mL/kg; > 20 kg	1,500 mL + 20 mL/kg; > 20 kg

The fasting deficit is calculated by multiplying the hourly maintenance fluid requirement by the number of hours of fluid restriction. It is recommended that 50% of the fasting deficit is replaced in the first hour and 25% in the second and third hours [896]. Berry (1986) proposed simplified guidelines for fluid administration according to the child's age and severity of surgical trauma [897] (Table 16).

Table 16: Intra-operative fluid management adapted for children fasted for six to eight hours, following the classical recommendation 'nil per oral after midnight'

Furman, <i>et al.</i> [896]			
Hour of fluid replacement	Maintenance fluid	Fasting deficit replacement	Persistent losses
First hour	As Table 14	50%	Third space + blood loss replacement
Second hour		25%	
Third hour		25%	
Berry [897]			
First hour	< 3 years: 25 mL/kg > 4 years: 15 mL/kg		Blood replacement 1:1 with blood or colloid or 3:1 with crystalloids
All other hours	Maintenance volume = 4 mL/kg/h Maintenance + mild trauma = 6 mL/kg/h Maintenance + moderate trauma = 8 mL/kg/h Maintenance + severe trauma = 10 mL/kg/h		Blood replacement 1:1 with blood or colloid or 3:1 with crystalloids

* Reduce the amount of fluid given during the first hour if children are fasting for a shorter period of time, or if the child was already being given intravenous fluid prior to surgery.

Five percent dextrose with one-quarter- to half-normal saline is often used as a maintenance fluid, while balanced salt solution or normal saline is used as replacement fluid. Blood losses are replaced with a 1:1 ratio of blood or colloid or a 3:1 ratio of crystalloid. However, the administration of a large volume of normal saline can cause dilutional acidosis or hyperchloremic acidosis, while a large volume of balanced salt solution, such as lactated Ringer's solution, can decrease serum osmolality, which is not beneficial in patients with decreased intracranial compliance. If appropriate, albumin, plasma, synthetic colloids, and blood should be administered [892].

Third-space losses may vary from 1 mL/kg/h for a minor surgical procedure to 15-20 mL/kg/h for major abdominal procedures, or even up to 50 mL/kg/h for surgery of necrotising enterocolitis in premature infants. Third-space losses should be replaced with crystalloids (normal saline or Ringer's lactate) [890].

Most of the fluids required during surgery are needed to replace fasting deficit or third-space losses, which are mainly extracellular fluids. Hydrating solutions should contain high concentrations of sodium and chloride and low concentrations of bicarbonate, calcium and potassium.

Intra-operative hypoglycaemia is rare in children. In contrast, hyperglycaemia is commonly encountered during anaesthesia and surgery. The replacement fluid should be free of dextrose or should not have > 1% dextrose. Current recommendations include the use of low-dextrose-containing solutions for maintenance fluid therapy, except in patients who are at high risk of hypoglycaemia [886, 895]. Intra-operative administration of glucose-free isotonic hydrating solutions should be the routine practice for most procedures in children over four to five years of age. In infants and young children, 5% dextrose solutions should be avoided, but it is appropriate to use 1% or 2% dextrose in lactated Ringer's solution [890].

3.19.2.3 Post-operative fluid management

During the post-operative period, the fundamental principle is to monitor gastrointestinal function and to continue oral or enteral nutrition as much as possible [887], while remembering that withholding oral fluids post-operatively from children undergoing day surgery helps prevent vomiting [898]. In minor surgical procedures, intra-operative administration of large volumes of crystalloids is associated with a reduced incidence of post-operative nausea and vomiting after anaesthesia in both paediatric and adult patients [899]. Berry's fluid replacement guidelines can be followed, provided the child is given lactated Ringer's solution or polyionique B66, which has an osmolality similar to plasma [900].

It is not obligatory to check serum chemistry after uncomplicated surgery in children with normal pre-operative renal and hepatic function. However, if oral intake has been postponed for > 24 hours (e.g. as in intestinal surgery), there is an increased risk of electrolyte abnormalities, requiring further assessment and subsequent management, particularly with potassium. Post-operative findings, such as decreased bowel movements and ileus, may be signs of hypokalemia, which may be corrected with a solution of 20 mmol/L potassium and an infusion rate of not more than 3 mmol/kg/day. The potassium should be given via peripheral venous access if the duration of infusion is not expected to exceed five days, or via central venous access when long-term parenteral nutrition is necessary.

The goals of fluid therapy are to provide basic metabolic requirements and to compensate for

gastrointestinal and additional losses. If hypovolemia is present, it should be treated rapidly. Hyponatremia is the most frequent electrolyte disorder in the post-operative period [900, 901]. This means that hypotonic fluid should not be routinely administered to hospitalised children because they have several stimuli for producing arginine vasopressin and are therefore at high risk for developing hyponatremia [890, 900, 902-905]. The preferred fluids for maintenance therapy are 0.45% saline with dextrose or isotonic fluids, in the absence of a specific indication for 0.25% saline. It is also advisable to administer isotonic fluids intra-operatively and also immediately post-operatively, albeit at two-thirds of the calculated maintenance rate in the recovery room. Fluid composition should balance high sodium requirements, energy requirements and solution osmolarity. The extra losses from gastric or chest tubes should be replaced with lactated Ringer's solution. Fluid that has been given to dilute medications must also be taken into account [890].

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention, especially due to the risk of polyuria as a result of post-obstructive diuresis. In children who develop polyuria, it is important to monitor fluid intake and urine output, as well as renal function and serum electrolytes. If necessary, clinicians should not hesitate in consulting with a paediatric nephrologist.

3.19.2.4 Post-operative fasting

It has been reported that fasting reduces the risk of vomiting by up to 50% [898, 906, 907]. However, a study found that if children were freely allowed to drink and eat when they felt ready or requested it, the incidence of vomiting did not increase and the children felt happier and were significantly less bothered by pain than children who were fasting [908]. The mean times until first drink and first eating in the children who were free to eat or drink were 108 and 270 minutes, respectively, which were four hours and three hours earlier than in the fasting group. Previous studies have suggested that gastric motility returns to normal one hour after emergence from anaesthesia in children who have undergone non-abdominal surgery [909]. The first oral intake in children at one hour after emergence from anaesthesia for minor surgery did not cause an increase in the incidence of vomiting, provided that the fluid ingested was at body temperature [910]. The EAU Panel members therefore recommend encouraging an early intake of fluid in children who have undergone minor or non-abdominal urological surgery.

3.19.3 Summary of evidence and recommendations for the management of post-operative fluid management

Summary of evidence	LE
Children are not simply smaller physiological versions of adults. They have their own unique metabolic features, which must be considered during surgery.	2

Recommendations	GR
Ensure that shorter pre-operative fasting periods apply for elective surgeries (up to four hours).	B
Use fluids with lower dextrose concentrations since hyperglycaemia is common in children, compared to intra-operative hypoglycaemia (which is very rare).	B
Do not routinely use hypotonic fluid in hospitalised children because they are at high risk of developing hyponatraemia.	A
Assess the baseline and daily levels of serum electrolytes, glucose, urea and/or creatinine in every child who receives intravenous fluids, especially in intestinal surgery (e.g. ileal augmentation), regardless of the type of solution chosen since there is an increased risk of electrolyte abnormalities in children undergoing such surgery.	B
Start early oral fluid intake in patients scheduled for minor surgical procedures.	A

3.20 Post-operative pain management: general information

3.20.1 Epidemiology, aetiology and pathophysiology

The provision of adequate pain control requires proper pain evaluation, accurate choice of drug and route of administration, and consideration of age, physical condition and type of surgery and anaesthesia [917]. However, there is still no standardised algorithm for management of post-operative pain in children [918]. There is an urgent need for a post-operative pain management protocol in children, particularly for guidance on the frequency of pain assessment, use of parenteral opioids, introduction of regional anaesthesia, and the application of rescue analgesics [919].

Traditional medical beliefs that neonates are incapable of experiencing pain have now been abandoned following recent and better understanding of how the pain system matures in humans, better pain assessment methods and a knowledge of the clinical consequences of pain in neonates [911, 920-923]. Many studies have indicated that deficient or insufficient analgesia may be the cause of future behavioural and

somatic sequelae [912, 924-926]. Our current understanding of pain management in children depends fully on the belief that all children, irrespective of age, deserve adequate treatment.

3.20.2 **Diagnostic evaluation**

Assessment of pain is the first step in pain management. Validated pain assessment tools are needed for this purpose and it is important to select the appropriate pain assessment technique. Several pain assessment tools have been developed according to the child's age, cultural background, mental status, communication skills and physiological reactions [927, 928].

One of the most important topics in paediatric pain management is informing and involving the child and parents during this process. Parents and patients can manage post-operative pain at home or in hospital if provided with the correct information. Parents and patients, if they are old enough, can actively take part in pain management in patient-family-controlled analgesia applications [913, 929-933].

3.20.3 **Disease management**

3.20.3.1 *Drugs and route of administration*

Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitisation occurs [934]. Local anaesthetics or non-steroidal analgesics are given intra-operatively to delay post-operative pain and to decrease post-operative analgesic consumption. Analgesics must be titrated until an appropriate response is achieved. Opioids can be administered to children by the oral, mucosal, transdermal, subcutaneous, intramuscular or intravenous routes [930]. The combination of opioids with nonsteroidal anti-inflammatory drugs (NSAIDs) or local anaesthetics (balanced or multimodal analgesia) can be used to increase the quality of analgesia and decrease undesired effects related to opioids [935]. The same combination of local anaesthetics, opioids, and non-opioid drugs used in adults can also be used in children taking into account their age, body weight and individual medical status.

The World Health Organization's 'pain ladder' is a useful tool for the pain management strategy [936]. A three-level strategy seems practical for clinical use. Post-operative management should be based on sufficient intra-operative pre-emptive analgesia with regional or caudal blockade followed by balanced analgesia.

Paracetamol and NSAIDs are the drugs of choice at the first level. As they become insufficient to prevent pain, weak and strong opioids are added to oral drugs to achieve balanced analgesia. Every institute must build their own strategy for post-operative analgesia. A proposed strategy for post-operative analgesia may be as follows:

1. Intra-operative regional or caudal block
2. Paracetamol + NSAID
3. Paracetamol + NSAID + weak opioid (e.g. tramadol or codeine)
4. Paracetamol + NSAID + strong opioid (e.g. morphine, fentanyl, oxycodone or pethidine)

3.20.3.2 *Circumcision*

Circumcision without anaesthesia, irrespective of age, is not recommended. Circumcision requires proper pain management [937]. Despite this, adequate pain management is still below expectation [938]. Potential analgesic interventions during circumcision include the use of a dorsal penile nerve block (DPNB) or ring block, topical anaesthetics (e.g. lidocaine-prilocaine cream, or 4% liposomal lidocaine cream), a less painful clamp (e.g. Mogen clamp), a pacifier, sucrose, and swaddling, preferably in combination [939-943].

Although DPNB and topical anaesthetics seem to have a similar post-operative analgesic effect, DPNB is still the most preferred method [944] (LE: 1a). Ultrasound guidance may improve the results, with an increase in procedural time [945, 946]. Caudal blockade methods have similar efficacy compared to DPNB. However, parents should be informed about the more frequent incidence of post-operative motor weakness and micturition problems [947-952].

3.20.3.3 *Penile, inguinal and scrotal surgery*

Caudal block is the most studied method for analgesia following surgery for hypospadias. Several agents with different doses, concentrations and administration techniques have been used with similar outcomes [953-967]. Both single and combined use of these agents is effective [954, 955, 957, 958, 963, 965].

Penile blocks can be used for post-operative analgesia and have similar post-operative analgesic properties as caudal blocks [968]. Two penile blocks at the beginning and end of surgery seems to provide better pain relief [969]. Severe bladder spasms caused by the presence of the bladder catheter may sometimes cause more problems than pain and is managed with antimuscarinic medications.

For inguinoscrotal surgery, all anaesthetic methods, such as caudal blocks [392, 970-972] nerve block [973, 974], wound infiltration or instillation, and irrigation with local anaesthetics [975-977] have been shown to have adequate post-operative analgesic properties. Combinations may improve the results [978].

Table 17: List of several drugs used in post-operative pain management in children [911-916]

Name	Route of administration	Dose	Side effects	General remarks	Caution
Non-narcotics					
Acetaminophen	Rectal	40 mg/kg loading, 20 mg/kg/dose 4 times/day	Nephrotoxicity, hepatotoxicity (neonates)	Most common used analgesic Antipyretic effect Opioid-sparing effect Wide safety range	Slow onset time and variable absorption via the rectal route; dividing the vehicle is not recommended. Total dose should not exceed: 100 mg/kg for children; 75 mg/kg for infants; 60 mg/kg for term and preterm neonates > 32 weeks post-conceptual age; and 40 mg/kg for preterm neonates < 32 weeks post-conceptual age
	Oral	15-40 mg/kg, followed by 30 mg/kg/8 h			
	Intravenous	Propacetamol (prodrug)			
Ibuprofen	Oral, rectal	4-10 mg/kg/dose 3-4 times/day		Better analgesic than paracetamol	Safety not established for infants < 6 months old
Diclofenac	Tablet, syrup, suppository	1-1.5 mg/kg 2-3 times/day	Nephrotoxicity, gastrointestinal disturbances	Better than ibuprofen	> 6 years old
Ketorolac	Oral, IV, IM	0.2-0.5 mg/kg every 6 h (48 h) Total dose < 2 mg/kg/day, maximum 5 days		Opioid-sparing effect	
Ketamine	Oral, rectal, IM, SC, IV, intraspinal	< 2 mg/kg (IM) < 1 mg/kg (IV, epidural)			
Metamizole, dipyrrone	Oral, IM Oral drop	10-15 mg/kg/dose (max 40 mg/kg total) 10-15 mg/kg 1 drop/kg/dose, up to 4 times/day	Risk of agranulocytosis, not clarified definitely	Very effective antipyretic	Not approved in some countries including USA, Sweden, Japan and Australia
Narcotics					
Opioids					
Tramadol (weak opioid)	Oral, rectal, IV, IM (dose can be repeated 4-6 times/day)	2-3 mg/kg/dose (oral, drop) 1-2 mg/kg/dose (oral, tablet) 1.5-3 mg/kg/dose (rectal) 0.75-2 mg/kg/dose (IM) 2-2.5 mg/kg/dose (IV) 0.1-0.25 mg/kg/h (continuous)	Nausea, vomiting, dyspepsia, constipation, urinary retention, respiratory depression, drowsiness, euphoria Nausea, vomiting, pruritus and rash	Does not inhibit prostaglandin synthesis	An IM injection is not recommended. Slow IV infusion. Be careful in patients taking psychoactive medications and with seizures

Codeine	Oral	1 mg/kg, single dose	Respiratory depression not seen after single dose	Both antitussive and analgesic effect	IM injection not recommended < 2 months old: be careful
Morphine	IM, IV	6-12 months: 0.1 mg/kg, IM 0.05 mg/kg, IV		Most commonly used opioid, but not the most suitable opioid for pain relief in children	
Nalbuphine	IV	< 3 months old: 0.05 mg/kg/dose > 3 months old: 0.05-0.10 mg/kg/dose (4-6 times/day)			
Piritramide	IV	0.05-0.10 mg/kg/dose (4-6 times/day)			
Dextromethorphan	Oral, syrup	1 mg/kg			
Pethidine/meperidine	IM, IV	1.5-2 mg/kg IM as premedicant 1 mg/kg IV as analgesic	No advantage over morphine		
Fentanyl	IV	1-2 µg/kg			
Buprenorphine	IV	3-5 mg/kg			
Pentazocine	IV, IM	1 mg/kg IM 0.5-0.75 mg/kg IV	In small infants, observe respiration after IV administration		
Regional (local) anaesthetics					
Bupivacaine		Maximum single bolus dose: 2.5-3.0 mg/kg Maximum infusion: 0.4-0.5 mg/kg/h (10-20 mg/kg/day) in older infants and children; 0.2-0.25 mg/kg/h (5-6 mg/kg/day) in neonates	Cardiotoxicity, convulsion		
Levobupivacaine	IV, IM	0.2-0.25% 1-2.5 mg/kg for single-shot epidural 0.2-0.4 mg/kg/h for IV continuous administration	Less toxic than bupivacaine		
Ropivacaine	IV, IM	0.2-0.25% 1-2.5 mg/kg for single-shot epidural 0.2-0.4 mg/kg/h for IV continuous administration	Less toxic than levobupivacaine		

3.20.3.4 Bladder and kidney surgery

Continuous epidural infusion of local anaesthetics [979-981], as well as systemic (intravenous) application of analgesics [982], has been shown to be effective. Ketorolac is an effective agent that is underused. It decreases the frequency and severity of bladder spasms and the length of post-operative hospital stay and costs [971, 983-986].

Open kidney surgery is particularly painful because all three muscle layers are cut during conventional loin incision. A dorsal lumbotomy incision may be a good alternative because of the shorter post-operative hospital stay and earlier return to oral intake and unrestricted daily activity [987].

Caudal blocks plus systemic analgesics [988], and continuous epidural analgesia, are effective in terms of decreased post-operative morphine requirement after renal surgery [989, 990]. However, when there is a relative contraindication to line insertion, a less experienced anaesthetist is available, or parents prefer it [991], non-invasive regimens composed of intra-operative and post-operative analgesics may be the choice. Particularly in this group of patients, stepwise analgesia protocols can be developed [992]. For laparoscopic approaches, intra-peritoneal spraying of local anaesthetic before incision of the perirenal fascia may be beneficial [993].

Table 18: A simple pain management strategy for paediatric urological surgery

Intensity of surgery	First step	Second step	Third step
Mild (inguinal, scrotal, penile)	Paracetamol and wound infiltration with local anaesthetics	non-steroidal anti-inflammatory drugs (NSAIDs)	Regional block/weak opioid or IV strong opioid with small increments as rescue analgesia (e.g. nalbuphine, fentanyl, meperidine, morphine)
Moderate (lower abdominal)			Peripheral nerve block (single shot or continuous infusion)/opioid injection (intravenous patient-controlled analgesia (IV PCA))
Severe (upper abdominal or lombotomy)			Epidural local/major peripheral nerve/plexus block/opioid injection (IV PCA)

3.20.4 Summary of evidence and recommendations for the management of post-operative pain

Summary of evidence	LE
Neonates experience pain.	3
Pain may cause behavioural and somatic sequelae.	3
Every institute must develop their own well-structured strategy for post-operative analgesia.	4

Recommendations	GR
Prevent/treat pain in children of all ages.	B
Evaluate pain using age-compatible assessment tools.	B
Inform patients and parents accurately.	B
Use pre-emptive and balanced analgesia in order to decrease the side effects of opioids.	B

4. REFERENCES

1. Stein, R., *et al.* Urinary tract infections in children: EAU/ESPU guidelines. *Eur Urol*, 2015. 67: 546. <https://www.ncbi.nlm.nih.gov/pubmed/25477258>
2. Tekgul, S., *et al.* EAU guidelines on vesicoureteral reflux in children. *Eur Urol*, 2012. 62: 534. <https://www.ncbi.nlm.nih.gov/pubmed/22698573>
3. Radmayr, C., *et al.* Management of undescended testes: European Association of Urology/European Society for Paediatric Urology Guidelines. *J Pediatr Urol*, 2016. <https://www.ncbi.nlm.nih.gov/pubmed/27687532>
4. Silay, M.S., *et al.* The role of antibiotic prophylaxis in antenatal hydronephrosis: A systematic review. *J Ped Urol*, 2017. prior to print

5. Phillips, B., *et al.* Oxford Centre for Evidence-Based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998. 2014.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
6. Gairdner, D. The fate of the foreskin, a study of circumcision. *Br Med J*, 1949. 2: 1433.
<https://www.ncbi.nlm.nih.gov/pubmed/15408299>
7. Kuehhas, F.E., *et al.* Incidence of balanitis xerotica obliterans in boys younger than 10 years presenting with phimosis. *Urol Int*, 2013. 90: 439.
<https://www.ncbi.nlm.nih.gov/pubmed/23296396>
8. Oster, J. Further fate of the foreskin. Incidence of preputial adhesions, phimosis, and smegma among Danish schoolboys. *Arch Dis Child*, 1968. 43: 200.
<https://www.ncbi.nlm.nih.gov/pubmed/5689532>
9. Chu, C.C., *et al.* Topical steroid treatment of phimosis in boys. *J Urol*, 1999. 162: 861.
<https://www.ncbi.nlm.nih.gov/pubmed/10458396>
10. Elmore, J.M., *et al.* Topical steroid therapy as an alternative to circumcision for phimosis in boys younger than 3 years. *J Urol*, 2002. 168: 1746.
<https://www.ncbi.nlm.nih.gov/pubmed/12352350>
11. ter Meulen, P.H., *et al.* A conservative treatment of phimosis in boys. *Eur Urol*, 2001. 40: 196.
<https://www.ncbi.nlm.nih.gov/pubmed/11528198>
12. Zavras, N., *et al.* Conservative treatment of phimosis with fluticasone propionate 0.05%: a clinical study in 1185 boys. *J Pediatr Urol*, 2009. 5: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/19097823>
13. Reddy, S., *et al.* Local steroid therapy as the first-line treatment for boys with symptomatic phimosis - a long-term prospective study. *Acta Paediatr*, 2012. 101: e130.
<https://www.ncbi.nlm.nih.gov/pubmed/22103624>
14. Golubovic, Z., *et al.* The conservative treatment of phimosis in boys. *Br J Urol*, 1996. 78: 786.
<https://www.ncbi.nlm.nih.gov/pubmed/8976781>
15. Pileggi, F.O., *et al.* Is suppression of hypothalamic-pituitary-adrenal axis significant during clinical treatment of phimosis? *J Urol*, 2010. 183: 2327.
<https://www.ncbi.nlm.nih.gov/pubmed/20400146>
16. Wu, X., *et al.* A report of 918 cases of circumcision with the Shang Ring: comparison between children and adults. *Urology*, 2013. 81: 1058.
<https://www.ncbi.nlm.nih.gov/pubmed/23465168>
17. Miernik, A., *et al.* Complete removal of the foreskin--why? *Urol Int*, 2011. 86: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/21474914>
18. Herndon, C.D., *et al.* A multicenter outcomes analysis of patients with neonatal reflux presenting with prenatal hydronephrosis. *J Urol*, 1999. 162: 1203.
<https://www.ncbi.nlm.nih.gov/pubmed/10458467>
19. Hiraoka, M., *et al.* Meatus tightly covered by the prepuce is associated with urinary infection. *Pediatr Int*, 2002. 44: 658.
<https://www.ncbi.nlm.nih.gov/pubmed/12421265>
20. To, T., *et al.* Cohort study on circumcision of newborn boys and subsequent risk of urinary-tract infection. *Lancet*, 1998. 352: 1813.
<https://www.ncbi.nlm.nih.gov/pubmed/9851381>
21. Wiswell, T.E. The prepuce, urinary tract infections, and the consequences. *Pediatrics*, 2000. 105: 860.
<https://www.ncbi.nlm.nih.gov/pubmed/10742334>
22. Ladenhauf, H.N., *et al.* Reduced bacterial colonisation of the glans penis after male circumcision in children--a prospective study. *J Pediatr Urol*, 2013. 9: 1137.
<https://www.ncbi.nlm.nih.gov/pubmed/23685114>
23. Larke, N.L., *et al.* Male circumcision and penile cancer: a systematic review and meta-analysis. *Cancer Causes Control*, 2011. 22: 1097.
<https://www.ncbi.nlm.nih.gov/pubmed/21695385>
24. American Academy of Pediatrics: Report of the Task Force on Circumcision. *Pediatrics*, 1999. 104: 388.
<https://www.ncbi.nlm.nih.gov/pubmed/2664697>
25. Thompson, H.C., *et al.* Report of the ad hoc task force on circumcision. *Pediatrics*, 1975. 56: 610.
<https://www.ncbi.nlm.nih.gov/pubmed/1174384>
26. Elalfy, M.S., *et al.* Risk of bleeding and inhibitor development after circumcision of previously untreated or minimally treated severe hemophilia A children. *Pediatr Hematol Oncol*, 2012. 29: 485.
<https://www.ncbi.nlm.nih.gov/pubmed/22866674>

27. Karaman, M.I., *et al.* Circumcision in bleeding disorders: improvement of our cost effective method with diathermic knife. *Urol J*, 2014. 11: 1406.
<https://www.ncbi.nlm.nih.gov/pubmed/24807751>
28. Christakis, D.A., *et al.* A trade-off analysis of routine newborn circumcision. *Pediatrics*, 2000. 105: 246.
<https://www.ncbi.nlm.nih.gov/pubmed/10617731>
29. Griffiths, D.M., *et al.* A prospective survey of the indications and morbidity of circumcision in children. *Eur Urol*, 1985. 11: 184.
<https://www.ncbi.nlm.nih.gov/pubmed/4029234>
30. Morris, B.J., *et al.* A 'snip' in time: what is the best age to circumcise? *BMC Pediatr*, 2012. 12: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/22373281>
31. Ross, J.H., Circumcision: Pro and con., in *Pediatric urology for the general urologist.*, J.S. Elder, Editor. 1996, Igaku-Shoin: New York.
32. Weiss, H.A., *et al.* Complications of circumcision in male neonates, infants and children: a systematic review. *BMC Urol*, 2010. 10: 2.
<https://www.ncbi.nlm.nih.gov/pubmed/20158883>
33. Anand, A., *et al.* Mannitol for paraphimosis reduction. *Urol Int*, 2013. 90: 106.
<https://www.ncbi.nlm.nih.gov/pubmed/23257575>
34. DeVries, C.R., *et al.* Reduction of paraphimosis with hyaluronidase. *Urology*, 1996. 48: 464.
<https://www.ncbi.nlm.nih.gov/pubmed/8804504>
35. Sijstermans, K., *et al.* The frequency of undescended testis from birth to adulthood: a review. *Int J Androl*, 2008. 31: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/17488243>
36. Berkowitz, G.S., *et al.* Prevalence and natural history of cryptorchidism. *Pediatrics*, 1993. 92: 44.
<https://www.ncbi.nlm.nih.gov/pubmed/8100060>
37. Kaefer, M., *et al.* The incidence of intersexuality in children with cryptorchidism and hypospadias: stratification based on gonadal palpability and meatal position. *J Urol*, 1999. 162: 1003.
<https://www.ncbi.nlm.nih.gov/pubmed/10458421>
38. Kollin, C., *et al.* Cryptorchidism: a clinical perspective. *Pediatr Endocrinol Rev*, 2014. 11 Suppl 2: 240.
<https://www.ncbi.nlm.nih.gov/pubmed/24683948>
39. Caesar, R.E., *et al.* The incidence of the cremasteric reflex in normal boys. *J Urol*, 1994. 152: 779.
<https://www.ncbi.nlm.nih.gov/pubmed/7912745>
40. Barthold, J.S., *et al.* The epidemiology of congenital cryptorchidism, testicular ascent and orchiopexy. *J Urol*, 2003. 170: 2396.
<https://www.ncbi.nlm.nih.gov/pubmed/14634436>
41. Turek, P.J., *et al.* The absent cryptorchid testis: surgical findings and their implications for diagnosis and etiology. *J Urol*, 1994. 151: 718.
<https://www.ncbi.nlm.nih.gov/pubmed/7905931>
42. Rabinowitz, R., *et al.* Late presentation of cryptorchidism: the etiology of testicular re-ascent. *J Urol*, 1997. 157: 1892.
<https://www.ncbi.nlm.nih.gov/pubmed/9112557>
43. Cendron, M., *et al.* Anatomical, morphological and volumetric analysis: a review of 759 cases of testicular maldescent. *J Urol*, 1993. 149: 570.
<https://www.ncbi.nlm.nih.gov/pubmed/8094761>
44. Braga, L.H., *et al.* Is there an optimal contralateral testicular cut-off size that predicts monorchism in boys with nonpalpable testicles? *J Pediatr Urol*, 2014. 10: 693.
<https://www.ncbi.nlm.nih.gov/pubmed/25008806>
45. Hurwitz, R.S., *et al.* How well does contralateral testis hypertrophy predict the absence of the nonpalpable testis? *J Urol*, 2001. 165: 588.
<https://www.ncbi.nlm.nih.gov/pubmed/11176443>
46. Elert, A., *et al.* Population-based investigation of familial undescended testis and its association with other urogenital anomalies. *J Pediatr Urol*, 2005. 1: 403.
<https://www.ncbi.nlm.nih.gov/pubmed/18947580>
47. Hrebinko, R.L., *et al.* The limited role of imaging techniques in managing children with undescended testes. *J Urol*, 1993. 150: 458.
<https://www.ncbi.nlm.nih.gov/pubmed/8100860>
48. Tasian, G.E., *et al.* Diagnostic performance of ultrasound in nonpalpable cryptorchidism: a systematic review and meta-analysis. *Pediatrics*, 2011. 127: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/21149435>

49. Elder, J.S. Ultrasonography is unnecessary in evaluating boys with a nonpalpable testis. *Pediatrics*, 2002. 110: 748.
<https://www.ncbi.nlm.nih.gov/pubmed/12359789>
50. Tasian, G.E., *et al.* Diagnostic imaging in cryptorchidism: utility, indications, and effectiveness. *J Pediatr Surg*, 2011. 46: 2406.
<https://www.ncbi.nlm.nih.gov/pubmed/22152893>
51. Wenzler, D.L., *et al.* What is the rate of spontaneous testicular descent in infants with cryptorchidism? *J Urol*, 2004. 171: 849.
<https://www.ncbi.nlm.nih.gov/pubmed/14713841>
52. Park, K.H., *et al.* Histological evidences suggest recommending orchiopexy within the first year of life for children with unilateral inguinal cryptorchid testis. *Int J Urol*, 2007. 14: 616.
<https://www.ncbi.nlm.nih.gov/pubmed/17645605>
53. Engeler, D.S., *et al.* Early orchiopexy: prepubertal intratubular germ cell neoplasia and fertility outcome. *Urology*, 2000. 56: 144.
<https://www.ncbi.nlm.nih.gov/pubmed/10869645>
54. Rajfer, J., *et al.* Hormonal therapy of cryptorchidism. A randomized, double-blind study comparing human chorionic gonadotropin and gonadotropin-releasing hormone. *N Engl J Med*, 1986. 314: 466.
<https://www.ncbi.nlm.nih.gov/pubmed/2868413>
55. Forest, M.G., *et al.* Undescended testis: comparison of two protocols of treatment with human chorionic gonadotropin. Effect on testicular descent and hormonal response. *Horm Res*, 1988. 30: 198.
<https://www.ncbi.nlm.nih.gov/pubmed/2907898>
56. Pyorala, S., *et al.* A review and meta-analysis of hormonal treatment of cryptorchidism. *J Clin Endocrinol Metab*, 1995. 80: 2795.
<https://www.ncbi.nlm.nih.gov/pubmed/7673426>
57. Lala, R., *et al.* Combined therapy with LHRH and HCG in cryptorchid infants. *Eur J Pediatr*, 1993. 152 Suppl 2: S31.
<https://www.ncbi.nlm.nih.gov/pubmed/8101810>
58. Forest, M.G., *et al.* Effects of human chorionic gonadotropin, androgens, adrenocorticotropin hormone, dexamethasone and hyperprolactinemia on plasma sex steroid-binding protein. *Ann N Y Acad Sci*, 1988. 538: 214.
<https://www.ncbi.nlm.nih.gov/pubmed/2847619>
59. Aycan, Z., *et al.* Evaluation of low-dose hCG treatment for cryptorchidism. *Turk J Pediatr*, 2006. 48: 228.
<https://www.ncbi.nlm.nih.gov/pubmed/17172066>
60. Hesse, V., *et al.* Three injections of human chorionic gonadotropin are as effective as ten injections in the treatment of cryptorchidism. *Horm Res*, 1988. 30: 193.
<https://www.ncbi.nlm.nih.gov/pubmed/2907897>
61. Hagberg, S., *et al.* Treatment of undescended testes with intranasal application of synthetic LH-RH. *Eur J Pediatr*, 1982. 139: 285.
<https://www.ncbi.nlm.nih.gov/pubmed/6133757>
62. Hadziselimovic, F., *et al.* Long-term effect of luteinizing hormone-releasing hormone analogue (buserelin) on cryptorchid testes. *J Urol*, 1987. 138: 1043.
<https://www.ncbi.nlm.nih.gov/pubmed/9258170>
63. Schwentner, C., *et al.* Neoadjuvant gonadotropin-releasing hormone therapy before surgery may improve the fertility index in undescended testes: a prospective randomized trial. *J Urol*, 2005. 173: 974.
<https://www.ncbi.nlm.nih.gov/pubmed/16600785>
64. Hadziselimovic, F., *et al.* Treatment with a luteinizing hormone-releasing hormone analogue after successful orchiopexy markedly improves the chance of fertility later in life. *J Urol*, 1997. 158: 1193.
<https://www.ncbi.nlm.nih.gov/pubmed/2888905>
65. Cortes, D., *et al.* Hormonal treatment may harm the germ cells in 1 to 3-year-old boys with cryptorchidism. *J Urol*, 2000. 163: 1290.
<https://www.ncbi.nlm.nih.gov/pubmed/10737531>
66. Ritzen, E.M. Undescended testes: a consensus on management. *Eur J Endocrinol*, 2008. 159 Suppl 1: S87.
<https://www.ncbi.nlm.nih.gov/pubmed/18728121>
67. Kollin, C., *et al.* Surgical treatment of unilaterally undescended testes: testicular growth after randomization to orchiopexy at age 9 months or 3 years. *J Urol*, 2007. 178: 1589.
<https://www.ncbi.nlm.nih.gov/pubmed/17707045>

68. Novaes, H.F., *et al.* Single scrotal incision orchiopexy - a systematic review. *Int Braz J Urol*, 2013. 39: 305.
<https://www.ncbi.nlm.nih.gov/pubmed/23849581>
69. Docimo, S.G. The results of surgical therapy for cryptorchidism: a literature review and analysis. *J Urol*, 1995. 154: 1148.
<https://www.ncbi.nlm.nih.gov/pubmed/7637073>
70. Ziyilan, O., *et al.* Failed orchiopexy. *Urol Int*, 2004. 73: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/15604574>
71. Prentiss, R.J., *et al.* Undescended testis: surgical anatomy of spermatic vessels, spermatic surgical triangles and lateral spermatic ligament. *J Urol*, 1960. 83: 686.
<https://www.ncbi.nlm.nih.gov/pubmed/14434738>
72. Kozminski, D.J., *et al.* Orchiopexy without Transparenchymal Fixation Suturing: A 29-Year Experience. *J Urol*, 2015. 194: 1743.
<https://www.ncbi.nlm.nih.gov/pubmed/26141850>
73. Martin, J.M., *et al.* Is radiotherapy a good adjuvant strategy for men with a history of cryptorchism and stage I seminoma? *Int J Radiat Oncol Biol Phys*, 2010. 76: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/19362785>
74. Na, S.W., *et al.* Single scrotal incision orchiopexy for children with palpable low-lying undescended testis: early outcome of a prospective randomized controlled study. *Korean J Urol*, 2011. 52: 637.
<https://www.ncbi.nlm.nih.gov/pubmed/22025961>
75. Parsons, J.K., *et al.* The low scrotal approach to the ectopic or ascended testicle: prevalence of a patent processus vaginalis. *J Urol*, 2003. 169: 1832.
<https://www.ncbi.nlm.nih.gov/pubmed/12686856>
76. Wayne, C., *et al.* What is the ideal surgical approach for intra-abdominal testes? A systematic review. *Pediatr Surg Int*, 2015. 31: 327.
<https://www.ncbi.nlm.nih.gov/pubmed/25663531>
77. Cortesi, N., *et al.* Diagnosis of bilateral abdominal cryptorchidism by laparoscopy. *Endoscopy*, 1976. 8: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/16743>
78. Jordan, G.H., *et al.* Laparoscopic single stage and staged orchiopexy. *J Urol*, 1994. 152: 1249.
<https://www.ncbi.nlm.nih.gov/pubmed/7915336>
79. Chandrasekharam, V.V. Laparoscopy vs inguinal exploration for nonpalpable undescended testis. *Indian J Pediatr*, 2005. 72: 1021.
<https://www.ncbi.nlm.nih.gov/pubmed/16388149>
80. Snodgrass, W.T., *et al.* Scrotal exploration for unilateral nonpalpable testis. *J Urol*, 2007. 178: 1718.
<https://www.ncbi.nlm.nih.gov/pubmed/17707015>
81. Cisek, L.J., *et al.* Current findings in diagnostic laparoscopic evaluation of the nonpalpable testis. *J Urol*, 1998. 160: 1145.
<https://www.ncbi.nlm.nih.gov/pubmed/9719296>
82. Patil, K.K., *et al.* Laparoscopy for impalpable testes. *BJU Int*, 2005. 95: 704.
<https://www.ncbi.nlm.nih.gov/pubmed/15784081>
83. Elderwy, A.A., *et al.* Laparoscopic versus open orchiopexy in the management of peeping testis: a multi-institutional prospective randomized study. *J Pediatr Urol*, 2014. 10: 605.
<https://www.ncbi.nlm.nih.gov/pubmed/25042877>
84. Kirsch, A.J., *et al.* Surgical management of the nonpalpable testis: the Children's Hospital of Philadelphia experience. *J Urol*, 1998. 159: 1340.
<https://www.ncbi.nlm.nih.gov/pubmed/9507881>
85. Fowler, R., *et al.* The role of testicular vascular anatomy in the salvage of high undescended testes. *Aust N Z J Surg*, 1959. 29: 92.
<https://www.ncbi.nlm.nih.gov/pubmed/13849840>
86. Koff, S.A., *et al.* Treatment of high undescended testes by low spermatic vessel ligation: an alternative to the Fowler-Stephens technique. *J Urol*, 1996. 156: 799.
<https://www.ncbi.nlm.nih.gov/pubmed/8683787>
87. Esposito, C., *et al.* Exploration of inguinal canal is mandatory in cases of non palpable testis if laparoscopy shows elements entering a closed inguinal ring. *Eur J Pediatr Surg*, 2010. 20: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/19746341>
88. Radmayr, C., *et al.* Long-term outcome of laparoscopically managed nonpalpable testes. *J Urol*, 2003. 170: 2409.
<https://www.ncbi.nlm.nih.gov/pubmed/14634439>

89. Baker, L.A., *et al.* A multi-institutional analysis of laparoscopic orchidopexy. *BJU Int*, 2001. 87: 484. <https://www.ncbi.nlm.nih.gov/pubmed/11298039>
90. Dave, S., *et al.* Open versus laparoscopic staged Fowler-Stephens orchiopexy: impact of long loop vas. *J Urol*, 2009. 182: 2435. <https://www.ncbi.nlm.nih.gov/pubmed/19765743>
91. Wacksman, J., *et al.* Laparoscopically assisted testicular autotransplantation for management of the intraabdominal undescended testis. *J Urol*, 1996. 156: 772. <https://www.ncbi.nlm.nih.gov/pubmed/8683780>
92. Penson, D., *et al.* Effectiveness of hormonal and surgical therapies for cryptorchidism: a systematic review. *Pediatrics*, 2013. 131: e1897. <https://www.ncbi.nlm.nih.gov/pubmed/23690511>
93. Koni, A., *et al.* Histopathological evaluation of orchiectomy specimens in 51 late postpubertal men with unilateral cryptorchidism. *J Urol*, 2014. 192: 1183. <https://www.ncbi.nlm.nih.gov/pubmed/24840535>
94. Trussell, J.C., *et al.* The relationship of cryptorchidism to fertility. *Curr Urol Rep*, 2004. 5: 142. <https://www.ncbi.nlm.nih.gov/pubmed/15028208>
95. Hadziselimovic, F., *et al.* The importance of both an early orchidopexy and germ cell maturation for fertility. *Lancet*, 2001. 358: 1156. <https://www.ncbi.nlm.nih.gov/pubmed/11597673>
96. Lee, P.A. Fertility after cryptorchidism: epidemiology and other outcome studies. *Urology*, 2005. 66: 427. <https://www.ncbi.nlm.nih.gov/pubmed/16098371>
97. Chua, M.E., *et al.* Hormonal therapy using gonadotropin releasing hormone for improvement of fertility index among children with cryptorchidism: a meta-analysis and systematic review. *J Pediatr Surg*, 2014. 49: 1659. <https://www.ncbi.nlm.nih.gov/pubmed/25475814>
98. Coughlin, M.T., *et al.* Age at unilateral orchiopexy: effect on hormone levels and sperm count in adulthood. *J Urol*, 1999. 162: 986. <https://www.ncbi.nlm.nih.gov/pubmed/10458417>
99. Tasian, G.E., *et al.* Age at orchiopexy and testis palpability predict germ and Leydig cell loss: clinical predictors of adverse histological features of cryptorchidism. *J Urol*, 2009. 182: 704. <https://www.ncbi.nlm.nih.gov/pubmed/19539332>
100. Dieckmann, K.P., *et al.* Clinical epidemiology of testicular germ cell tumors. *World J Urol*, 2004. 22: 2. <https://www.ncbi.nlm.nih.gov/pubmed/15034740>
101. Pettersson, A., *et al.* Age at surgery for undescended testis and risk of testicular cancer. *N Engl J Med*, 2007. 356: 1835. <https://www.ncbi.nlm.nih.gov/pubmed/17476009>
102. Walsh, T.J., *et al.* Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer. *J Urol*, 2007. 178: 1440. <https://www.ncbi.nlm.nih.gov/pubmed/17706709>
103. Kapur, P., *et al.* Pediatric hernias and hydroceles. *Pediatr Clin North Am*, 1998. 45: 773. <https://www.ncbi.nlm.nih.gov/pubmed/9728185>
104. Barthold, J.S., Abnormalities of the testis and scrotum and their surgical management, in Campbell-Walsh Urology, A.J. Wein & e. al., Eds. 2012, Elsevier Saunders: Philadelphia.
105. Schneck, F.X., *et al.*, Abnormalities of the testes and scrotum and their surgical management in Campbell's Urology, 2002, WB Saunders: Philadelphia.
106. Rubenstein, R.A., *et al.* Benign intrascrotal lesions. *J Urol*, 2004. 171: 1765. <https://www.ncbi.nlm.nih.gov/pubmed/15076274>
107. Lin, H.C., *et al.* Testicular teratoma presenting as a transilluminating scrotal mass. *Urology*, 2006. 67: 1290.e3. <https://www.ncbi.nlm.nih.gov/pubmed/16750249>
108. Skoog, S.J. Benign and malignant pediatric scrotal masses. *Pediatr Clin North Am*, 1997. 44: 1229. <https://www.ncbi.nlm.nih.gov/pubmed/9326960>
109. Koski, M.E., *et al.* Infant communicating hydroceles--do they need immediate repair or might some clinically resolve? *J Pediatr Surg*, 2010. 45: 590. <https://www.ncbi.nlm.nih.gov/pubmed/20223325>
110. Stringer, M.D., *et al.*, Patent processus vaginalis., in Pediatric urology, 2001, WB Saunders: Philadelphia.

111. Stylianos, S., *et al.* Incarceration of inguinal hernia in infants prior to elective repair. *J Pediatr Surg*, 1993. 28: 582.
<https://www.ncbi.nlm.nih.gov/pubmed/8483072>
112. Hall, N.J., *et al.* Surgery for hydrocele in children—an avoidable excess? *J Pediatr Surg*, 2011. 46: 2401.
<https://www.ncbi.nlm.nih.gov/pubmed/22152892>
113. Saad, S., *et al.* Ten-year review of groin laparoscopy in 1001 pediatric patients with clinical unilateral inguinal hernia: an improved technique with transhernia multiple-channel scope. *J Pediatr Surg*, 2011. 46: 1011.
<https://www.ncbi.nlm.nih.gov/pubmed/21616272>
114. Christensen, T., *et al.* New onset of hydroceles in boys over 1 year of age. *Int J Urol*, 2006. 13: 1425.
<https://www.ncbi.nlm.nih.gov/pubmed/17083397>
115. Cavusoglu, Y.H., *et al.* Acute scrotum -- etiology and management. *Indian J Pediatr*, 2005. 72: 201.
<https://www.ncbi.nlm.nih.gov/pubmed/15812112>
116. Klin, B., *et al.* Epididymitis in childhood: a clinical retrospective study over 5 years. *Isr Med Assoc J*, 2001. 3: 833.
<https://www.ncbi.nlm.nih.gov/pubmed/11729579>
117. Makela, E., *et al.* A 19-year review of paediatric patients with acute scrotum. *Scand J Surg*, 2007. 96: 62.
<https://www.ncbi.nlm.nih.gov/pubmed/17461315>
118. McAndrew, H.F., *et al.* The incidence and investigation of acute scrotal problems in children. *Pediatr Surg Int*, 2002. 18: 435.
<https://www.ncbi.nlm.nih.gov/pubmed/12415374>
119. Sakellaris, G.S., *et al.* Acute epididymitis in Greek children: a 3-year retrospective study. *Eur J Pediatr*, 2008. 167: 765.
<https://www.ncbi.nlm.nih.gov/pubmed/17786475>
120. Varga, J., *et al.* Acute scrotal pain in children--ten years' experience. *Urol Int*, 2007. 78: 73.
<https://www.ncbi.nlm.nih.gov/pubmed/17192737>
121. Bingol-Kologlu, M., *et al.* An exceptional complication following appendectomy: acute inguinal and scrotal suppuration. *Int Urol Nephrol*, 2006. 38: 663.
<https://www.ncbi.nlm.nih.gov/pubmed/17160451>
122. Dayanir, Y.O., *et al.* Epididymo-orchitis mimicking testicular torsion in Henoch-Schonlein purpura. *Eur Radiol*, 2001. 11: 2267.
<https://www.ncbi.nlm.nih.gov/pubmed/11702171>
123. Diamond, D.A., *et al.* Neonatal scrotal haematoma: mimicker of neonatal testicular torsion. *BJU Int*, 2003. 91: 675.
<https://www.ncbi.nlm.nih.gov/pubmed/12699483>
124. Ha, T.S., *et al.* Scrotal involvement in childhood Henoch-Schonlein purpura. *Acta Paediatr*, 2007. 96: 552.
<https://www.ncbi.nlm.nih.gov/pubmed/17306010>
125. Hara, Y., *et al.* Acute scrotum caused by Henoch-Schonlein purpura. *Int J Urol*, 2004. 11: 578.
<https://www.ncbi.nlm.nih.gov/pubmed/15242376>
126. Klin, B., *et al.* Acute idiopathic scrotal edema in children--revisited. *J Pediatr Surg*, 2002. 37: 1200.
<https://www.ncbi.nlm.nih.gov/pubmed/12149702>
127. Krause, W. Is acute idiopathic scrotal edema in children a special feature of neutrophilic eccrine hidradenitis? *Dermatology*, 2004. 208: 86; author reply 86.
<https://www.ncbi.nlm.nih.gov/pubmed/14730248>
128. Matsumoto, A., *et al.* Torsion of the hernia sac within a hydrocele of the scrotum in a child. *Int J Urol*, 2004. 11: 789.
<https://www.ncbi.nlm.nih.gov/pubmed/15379947>
129. Myers, J.B., *et al.* Torsion of an indirect hernia sac causing acute scrotum. *J Pediatr Surg*, 2004. 39: 122.
<https://www.ncbi.nlm.nih.gov/pubmed/14694389>
130. Ng, K.H., *et al.* An unusual presentation of acute scrotum after appendicitis. *Singapore Med J*, 2002. 43: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/12437045>
131. Singh, S., *et al.* Acute scrotum in children: a rare presentation of acute, non-perforated appendicitis. *Pediatr Surg Int*, 2003. 19: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/12682749>

132. van Langen, A.M., *et al.* Acute idiopathic scrotal oedema: four cases and a short review. *Eur J Pediatr*, 2001. 160: 455.
<https://www.ncbi.nlm.nih.gov/pubmed/11475590>
133. Vlazakis, S., *et al.* Right acute hemiscrotum caused by insertion of an inflamed appendix. *BJU Int*, 2002. 89: 967.
<https://www.ncbi.nlm.nih.gov/pubmed/12010250>
134. D'Andrea, A., *et al.* US in the assessment of acute scrotum. *Crit Ultrasound J*, 2013. 5: S8.
<http://www.criticalultrasoundjournal.com/content/5/S1/S8>
135. Davis, J.E., *et al.* Scrotal emergencies. *Emerg Med Clin North Am*, 2011. 29: 469.
<https://www.ncbi.nlm.nih.gov/pubmed/21782069>
136. Jimoh, B.M., *et al.* Idiopathic scrotal hematoma in neonate: a case report and review of the literature. *Case Rep Urol*, 2014. 2014: 212914.
<https://www.ncbi.nlm.nih.gov/pubmed/24982811>
137. Matzek, B.A., *et al.* Traumatic testicular dislocation after minor trauma in a pediatric patient. *J Emerg Med*, 2013. 45: 537.
<https://www.ncbi.nlm.nih.gov/pubmed/23899815>
138. Wright, S., *et al.* Emergency ultrasound of acute scrotal pain. *Eur J Emerg Med*, 2015. 22: 2.
<https://www.ncbi.nlm.nih.gov/pubmed/24910960>
139. Yusuf, G.T., *et al.* A review of ultrasound imaging in scrotal emergencies. *J Ultrasound*, 2013. 16: 171.
<https://www.ncbi.nlm.nih.gov/pubmed/24432171>
140. Remer, E.M., *et al.* ACR Appropriateness Criteria (R) acute onset of scrotal pain--without trauma, without antecedent mass. *Ultrasound Q*, 2012. 28: 47.
<https://www.ncbi.nlm.nih.gov/pubmed/22357246>
141. Kadish, H.A., *et al.* A retrospective review of pediatric patients with epididymitis, testicular torsion, and torsion of testicular appendages. *Pediatrics*, 1998. 102: 73.
<https://www.ncbi.nlm.nih.gov/pubmed/9651416>
142. Sauvat, F., *et al.* [Age for testicular torsion?]. *Arch Pediatr*, 2002. 9: 1226.
<https://www.ncbi.nlm.nih.gov/pubmed/12536102>
143. Somekh, E., *et al.* Acute epididymitis in boys: evidence of a post-infectious etiology. *J Urol*, 2004. 171: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/14665940>
144. Yerkes, E.B., *et al.* Management of perinatal torsion: today, tomorrow or never? *J Urol*, 2005. 174: 1579.
<https://www.ncbi.nlm.nih.gov/pubmed/16148656>
145. Boettcher, M., *et al.* Clinical and sonographic features predict testicular torsion in children: a prospective study. *BJU Int*, 2013. 112: 1201.
<https://www.ncbi.nlm.nih.gov/pubmed/23826981>
146. Nelson, C.P., *et al.* The cremasteric reflex: a useful but imperfect sign in testicular torsion. *J Pediatr Surg*, 2003. 38: 1248.
<https://www.ncbi.nlm.nih.gov/pubmed/23826981>
147. Mushtaq, I., *et al.* Retrospective review of paediatric patients with acute scrotum. *ANZ J Surg*, 2003. 73: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/12534742>
148. Murphy, F.L., *et al.* Early scrotal exploration in all cases is the investigation and intervention of choice in the acute paediatric scrotum. *Pediatr Surg Int*, 2006. 22: 413.
<https://www.ncbi.nlm.nih.gov/pubmed/16602024>
149. Baker, L.A., *et al.* An analysis of clinical outcomes using color doppler testicular ultrasound for testicular torsion. *Pediatrics*, 2000. 105: 604.
<https://www.ncbi.nlm.nih.gov/pubmed/10699116>
150. Gunther, P., *et al.* Acute testicular torsion in children: the role of sonography in the diagnostic workup. *Eur Radiol*, 2006. 16: 2527.
<https://www.ncbi.nlm.nih.gov/pubmed/16724203>
151. Kalfa, N., *et al.* Multicenter assessment of ultrasound of the spermatic cord in children with acute scrotum. *J Urol*, 2007. 177: 297.
<https://www.ncbi.nlm.nih.gov/pubmed/17162068>
152. Karmazyn, B., *et al.* Clinical and sonographic criteria of acute scrotum in children: a retrospective study of 172 boys. *Pediatr Radiol*, 2005. 35: 302.
<https://www.ncbi.nlm.nih.gov/pubmed/15503003>

153. Lam, W.W., *et al.* Colour Doppler ultrasonography replacing surgical exploration for acute scrotum: myth or reality? *Pediatr Radiol*, 2005. 35: 597.
<https://www.ncbi.nlm.nih.gov/pubmed/15761770>
154. Schalamon, J., *et al.* Management of acute scrotum in children--the impact of Doppler ultrasound. *J Pediatr Surg*, 2006. 41: 1377.
<https://www.ncbi.nlm.nih.gov/pubmed/16863840>
155. Pepe, P., *et al.* Does color Doppler sonography improve the clinical assessment of patients with acute scrotum? *Eur J Radiol*, 2006. 60: 120.
<https://www.ncbi.nlm.nih.gov/pubmed/16730939>
156. Kalfa, N., *et al.* Ultrasonography of the spermatic cord in children with testicular torsion: impact on the surgical strategy. *J Urol*, 2004. 172: 1692.
<https://www.ncbi.nlm.nih.gov/pubmed/15371792>
157. Nussbaum Blask, A.R., *et al.* Color Doppler sonography and scintigraphy of the testis: a prospective, comparative analysis in children with acute scrotal pain. *Pediatr Emerg Care*, 2002. 18: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/11973493>
158. Paltiel, H.J., *et al.* Acute scrotal symptoms in boys with an indeterminate clinical presentation: comparison of color Doppler sonography and scintigraphy. *Radiology*, 1998. 207: 223.
<http://pubs.rsna.org/doi/abs/10.1148/radiology.207.1.9530319>
159. Terai, A., *et al.* Dynamic contrast-enhanced subtraction magnetic resonance imaging in diagnostics of testicular torsion. *Urology*, 2006. 67: 1278.
<https://www.ncbi.nlm.nih.gov/pubmed/16765192>
160. Yuan, Z., *et al.* Clinical study of scrotum scintigraphy in 49 patients with acute scrotal pain: a comparison with ultrasonography. *Ann Nucl Med*, 2001. 15: 225.
<https://www.ncbi.nlm.nih.gov/pubmed/11545192>
161. Karmazyn, B., *et al.* Duplex sonographic findings in children with torsion of the testicular appendages: overlap with epididymitis and epididymo-orchitis. *J Pediatr Surg*, 2006. 41: 500.
<https://www.ncbi.nlm.nih.gov/pubmed/16516624>
162. Lau, P., *et al.* Acute epididymitis in boys: are antibiotics indicated? *Br J Urol*, 1997. 79: 797.
<https://www.ncbi.nlm.nih.gov/pubmed/9158522>
163. Abul, F., *et al.* The acute scrotum: a review of 40 cases. *Med Princ Pract*, 2005. 14: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/15863992>
164. Cornel, E.B., *et al.* Manual derotation of the twisted spermatic cord. *BJU Int*, 1999. 83: 672.
<https://www.ncbi.nlm.nih.gov/pubmed/10233577>
165. Garel, L., *et al.* Preoperative manual detorsion of the spermatic cord with Doppler ultrasound monitoring in patients with intravaginal acute testicular torsion. *Pediatr Radiol*, 2000. 30: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/10663509>
166. Sessions, A.E., *et al.* Testicular torsion: direction, degree, duration and disinformation. *J Urol*, 2003. 169: 663.
<https://www.ncbi.nlm.nih.gov/pubmed/12544339>
167. Visser, A.J., *et al.* Testicular function after torsion of the spermatic cord. *BJU Int*, 2003. 92: 200.
<https://www.ncbi.nlm.nih.gov/pubmed/12887467>
168. Tryfonas, G., *et al.* Late postoperative results in males treated for testicular torsion during childhood. *J Pediatr Surg*, 1994. 29: 553.
<https://www.ncbi.nlm.nih.gov/pubmed/8014814>
169. Anderson, M.J., *et al.* Semen quality and endocrine parameters after acute testicular torsion. *J Urol*, 1992. 147: 1545.
<https://www.ncbi.nlm.nih.gov/pubmed/1593686>
170. Arap, M.A., *et al.* Late hormonal levels, semen parameters, and presence of antisperm antibodies in patients treated for testicular torsion. *J Androl*, 2007. 28: 528.
<https://www.ncbi.nlm.nih.gov/pubmed/17287456>
171. Mor, Y., *et al.* Testicular fixation following torsion of the spermatic cord--does it guarantee prevention of recurrent torsion events? *J Urol*, 2006. 175: 171.
<https://www.ncbi.nlm.nih.gov/pubmed/16406900>
172. Figueroa, V., *et al.* Comparative analysis of detorsion alone versus detorsion and tunica albuginea decompression (fasciotomy) with tunica vaginalis flap coverage in the surgical management of prolonged testicular ischemia. *J Urol*, 2012. 188: 1417.
<https://www.ncbi.nlm.nih.gov/pubmed/22906680>

173. Akcora, B., *et al.* The protective effect of darbepoetin alfa on experimental testicular torsion and detorsion injury. *Int J Urol*, 2007. 14: 846.
<https://www.ncbi.nlm.nih.gov/pubmed/17760753>
174. Aksoy, H., *et al.* Dehydroepiandrosterone treatment attenuates reperfusion injury after testicular torsion and detorsion in rats. *J Pediatr Surg*, 2007. 42: 1740.
<https://www.ncbi.nlm.nih.gov/pubmed/17923206>
175. Haj, M., *et al.* Effect of external scrotal cooling on the viability of the testis with torsion in rats. *Eur Surg Res*, 2007. 39: 160.
<https://www.ncbi.nlm.nih.gov/pubmed/17341878>
176. Unal, D., *et al.* Protective effects of trimetazidine on testicular ischemia-reperfusion injury in rats. *Urol Int*, 2007. 78: 356.
<https://www.ncbi.nlm.nih.gov/pubmed/17495496>
177. Yazihan, N., *et al.* Protective role of erythropoietin during testicular torsion of the rats. *World J Urol*, 2007. 25: 531.
<https://www.ncbi.nlm.nih.gov/pubmed/17690891>
178. Lian, B.S., *et al.* Factors Predicting Testicular Atrophy after Testicular Salvage following Torsion. *Eur J Pediatr Surg*, 2016. 26: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/26509312>
179. Philip, J., *et al.* Mumps orchitis in the non-immune postpubertal male: a resurgent threat to male fertility? *BJU Int*, 2006. 97: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/16336344>
180. Gielchinsky, I., *et al.* Pregnancy Rates after Testicular Torsion. *J Urol*, 2016. 196: 852.
<https://www.ncbi.nlm.nih.gov/pubmed/27117442>
181. Bergman, J.E., *et al.* Epidemiology of hypospadias in Europe: a registry-based study. *World J Urol*, 2015. 33: 2159.
<https://www.ncbi.nlm.nih.gov/pubmed/25712311>
182. Morera, A.M., *et al.* A study of risk factors for hypospadias in the Rhone-Alpes region (France). *J Pediatr Urol*, 2006. 2: 169.
<https://www.ncbi.nlm.nih.gov/pubmed/18947603>
183. van der Zanden, L.F., *et al.* Exploration of gene-environment interactions, maternal effects and parent of origin effects in the etiology of hypospadias. *J Urol*, 2012. 188: 2354.
<https://www.ncbi.nlm.nih.gov/pubmed/23088992>
184. Springer, A., *et al.* Worldwide prevalence of hypospadias. *J Pediatr Urol*, 2016. 12: 152 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/26810252>
185. Fredell, L., *et al.* Heredity of hypospadias and the significance of low birth weight. *J Urol*, 2002. 167: 1423.
<https://www.ncbi.nlm.nih.gov/pubmed/11832761>
186. Lund, L., *et al.* Prevalence of hypospadias in Danish boys: a longitudinal study, 1977-2005. *Eur Urol*, 2009. 55: 1022.
<https://www.ncbi.nlm.nih.gov/pubmed/19155122>
187. Mouriquand, O.D., *et al.*, Hypospadias., in *Pediatric Urology*, 2001, WB Saunders: Philadelphia.
188. van Rooij, I.A., *et al.* Risk factors for different phenotypes of hypospadias: results from a Dutch case-control study. *BJU Int*, 2013. 112: 121.
<https://www.ncbi.nlm.nih.gov/pubmed/23305310>
189. Norgaard, M., *et al.* Maternal use of oral contraceptives during early pregnancy and risk of hypospadias in male offspring. *Urology*, 2009. 74: 583.
<https://www.ncbi.nlm.nih.gov/pubmed/19592074>
190. Netto, J.M., *et al.* Hormone therapy in hypospadias surgery: a systematic review. *J Pediatr Urol*, 2013. 9: 971.
<https://www.ncbi.nlm.nih.gov/pubmed/23602841>
191. Chariatte, V., *et al.* Uroradiological screening for upper and lower urinary tract anomalies in patients with hypospadias: a systematic literature review. *Evid Based Med*, 2013. 18: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/22815315>
192. Belman, A.B., Hypospadias and chordee, in *Clinical Pediatric Urology 2002*, Martin Dunitz: London.
193. Malik, R.D., *et al.* Survey of pediatric urologists on the preoperative use of testosterone in the surgical correction of hypospadias. *J Pediatr Urol*, 2014.
<https://www.ncbi.nlm.nih.gov/pubmed/24726783>
194. Wright, I., *et al.* Effect of preoperative hormonal stimulation on postoperative complication rates after proximal hypospadias repair: a systematic review. *J Urol*, 2013. 190: 652.
<https://www.ncbi.nlm.nih.gov/pubmed/23597451>

195. Kaya, C., *et al.* The role of pre-operative androgen stimulation in hypospadias surgery. *Transl Androl Urol*, 2014. 3: 340.
<https://www.ncbi.nlm.nih.gov/pubmed/26816790>
196. Bush, N.C., *et al.* Age does not impact risk for urethroplasty complications after tubularized incised plate repair of hypospadias in prepubertal boys. *J Pediatr Urol*, 2013. 9: 252.
<https://www.ncbi.nlm.nih.gov/pubmed/22542204>
197. Perlmutter, A.E., *et al.* Impact of patient age on distal hypospadias repair: a surgical perspective. *Urology*, 2006. 68: 648.
<https://www.ncbi.nlm.nih.gov/pubmed/16979730>
198. Bhat, A., *et al.* Comparison of variables affecting the surgical outcomes of tubularized incised plate urethroplasty in adult and pediatric hypospadias. *J Pediatr Urol*, 2016. 12: 108 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/26778183>
199. Castagnetti, M., *et al.* Surgical management of primary severe hypospadias in children: systematic 20-year review. *J Urol*, 2010. 184: 1469.
<https://www.ncbi.nlm.nih.gov/pubmed/20727541>
200. Baskin, L.S., *et al.* Changing concepts of hypospadias curvature lead to more onlay island flap procedures. *J Urol*, 1994. 151: 191.
<https://www.ncbi.nlm.nih.gov/pubmed/8254812>
201. Hollowell, J.G., *et al.* Preservation of the urethral plate in hypospadias repair: extended applications and further experience with the onlay island flap urethroplasty. *J Urol*, 1990. 143: 98.
<https://www.ncbi.nlm.nih.gov/pubmed/2294275>
202. Snodgrass, W., *et al.* Straightening ventral curvature while preserving the urethral plate in proximal hypospadias repair. *J Urol*, 2009. 182: 1720.
<https://www.ncbi.nlm.nih.gov/pubmed/19692004>
203. Braga, L.H., *et al.* Ventral penile lengthening versus dorsal plication for severe ventral curvature in children with proximal hypospadias. *J Urol*, 2008. 180: 1743.
<https://www.ncbi.nlm.nih.gov/pubmed/18721961>
204. el-Kassaby, A.W., *et al.* Modified tubularized incised plate urethroplasty for hypospadias repair: a long-term results of 764 patients. *Urology*, 2008. 71: 611.
<https://www.ncbi.nlm.nih.gov/pubmed/18295308>
205. El-Sherbiny, M.T., *et al.* Comprehensive analysis of tubularized incised-plate urethroplasty in primary and re-operative hypospadias. *BJU Int*, 2004. 93: 1057.
<https://www.ncbi.nlm.nih.gov/pubmed/15142164>
206. Orkiszewski, M., *et al.* Morphology and urodynamics after longitudinal urethral plate incision in proximal hypospadias repairs: long-term results. *Eur J Pediatr Surg*, 2004. 14: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/15024677>
207. Snodgrass, W.T., *et al.* Tubularized incised plate hypospadias repair for distal hypospadias. *J Pediatr Urol*, 2010. 6: 408.
<https://www.ncbi.nlm.nih.gov/pubmed/17222659>
208. Pfistermuller, K.L., *et al.* Meta-analysis of complication rates of the tubularized incised plate (TIP) repair. *J Pediatr Urol*, 2015. 11: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/25819601>
209. Schwentner, C., *et al.* Interim outcome of the single stage dorsal inlay skin graft for complex hypospadias reoperations. *J Urol*, 2006. 175: 1872.
<https://www.ncbi.nlm.nih.gov/pubmed/16600785>
210. Ahmed, M., *et al.* Is combined inner preputial inlay graft with tubularized incised plate in hypospadias repair worth doing? *J Pediatr Urol*, 2015. 11: 229 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/26119452>
211. Pippi Salle, J.L., *et al.* Proximal hypospadias: A persistent challenge. Single institution outcome analysis of three surgical techniques over a 10-year period. *J Pediatr Urol*, 2016. 12: 28 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/26279102>
212. Meyer-Junghanel, L., *et al.* Experience with repair of 120 hypospadias using Mathieu's procedure. *Eur J Pediatr Surg*, 1995. 5: 355.
<https://www.ncbi.nlm.nih.gov/pubmed/8773227>
213. Snodgrass, W.T., *et al.* Urethral strictures following urethral plate and proximal urethral elevation during proximal TIP hypospadias repair. *J Pediatr Urol*, 2013. 9: 990.
<https://www.ncbi.nlm.nih.gov/pubmed/23707201>
214. Cambareri, G.M., *et al.* Hypospadias repair with onlay preputial graft: a 25-year experience with long-term follow-up. *BJU Int*, 2016. 118: 451.
<https://www.ncbi.nlm.nih.gov/pubmed/26780179>

215. Perovic, S., *et al.* Onlay island flap urethroplasty for severe hypospadias: a variant of the technique. *J Urol*, 1994. 151: 711.
<https://www.ncbi.nlm.nih.gov/pubmed/8308994>
216. Kocvara, R., *et al.* Inlay-onlay flap urethroplasty for hypospadias and urethral stricture repair. *J Urol*, 1997. 158: 2142.
<https://www.ncbi.nlm.nih.gov/pubmed/9366331>
217. Castagnetti, M., *et al.* Primary severe hypospadias: comparison of reoperation rates and parental perception of urinary symptoms and cosmetic outcomes among 4 repairs. *J Urol*, 2013. 189: 1508.
<https://www.ncbi.nlm.nih.gov/pubmed/23154207>
218. Koyanagi, T., *et al.* One-stage repair of hypospadias: is there no simple method universally applicable to all types of hypospadias? *J Urol*, 1994. 152: 1232.
<https://www.ncbi.nlm.nih.gov/pubmed/8072111>
219. Hayashi, Y., *et al.* Neo-modified Koyanagi technique for the single-stage repair of proximal hypospadias. *J Pediatr Urol*, 2007. 3: 239.
<https://www.ncbi.nlm.nih.gov/pubmed/18947743>
220. Catti, M., *et al.* Original Koyanagi urethroplasty versus modified Hayashi technique: outcome in 57 patients. *J Pediatr Urol*, 2009. 5: 300.
<https://www.ncbi.nlm.nih.gov/pubmed/19457720>
221. DeFoor, W., *et al.* Results of single staged hypospadias surgery to repair penoscrotal hypospadias with bifid scrotum or penoscrotal transposition. *J Urol*, 2003. 170: 1585.
<https://www.ncbi.nlm.nih.gov/pubmed/14501667>
222. Bracka, A. Hypospadias repair: the two-stage alternative. *Br J Urol*, 1995. 76 Suppl 3: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/8535768>
223. Lam, P.N., *et al.* 2-stage repair in infancy for severe hypospadias with chordee: long-term results after puberty. *J Urol*, 2005. 174: 1567.
<https://www.ncbi.nlm.nih.gov/pubmed/16148653>
224. Stanasel, I., *et al.* Complications following Staged Hypospadias Repair Using Transposed Preputial Skin Flaps. *J Urol*, 2015. 194: 512.
<https://www.ncbi.nlm.nih.gov/pubmed/25701546>
225. Ahmed, S., *et al.* Buccal mucosal graft for secondary hypospadias repair and urethral replacement. *Br J Urol*, 1997. 80: 328.
<https://www.ncbi.nlm.nih.gov/pubmed/9284210>
226. Mokhless, I.A., *et al.* The multistage use of buccal mucosa grafts for complex hypospadias: histological changes. *J Urol*, 2007. 177: 1496.
<https://www.ncbi.nlm.nih.gov/pubmed/17382762>
227. Castagnetti, M., *et al.* Does Preputial Reconstruction Increase Complication Rate of Hypospadias Repair? 20-Year Systematic Review and Meta-Analysis. *Front Pediatr*, 2016. 4: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/27200322>
228. Hsieh, M.H., *et al.* Surgical antibiotic practices among pediatric urologists in the United States. *J Pediatr Urol*, 2011. 7: 192.
<https://www.ncbi.nlm.nih.gov/pubmed/20537590>
229. Chalmers, D.J., *et al.* Distal hypospadias repair in infants without a postoperative stent. *Pediatr Surg Int*, 2015. 31: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/25475503>
230. Meir, D.B., *et al.* Is prophylactic antimicrobial treatment necessary after hypospadias repair? *J Urol*, 2004. 171: 2621.
<https://www.ncbi.nlm.nih.gov/pubmed/15118434>
231. Kanaroglou, N., *et al.* Is there a role for prophylactic antibiotics after stented hypospadias repair? *J Urol*, 2013. 190: 1535.
<https://www.ncbi.nlm.nih.gov/pubmed/23416639>
232. Bush, N.C., *et al.* Glans size is an independent risk factor for urethroplasty complications after hypospadias repair. *J Pediatr Urol*, 2015. 11: 355 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/26320396>
233. Lee, O.T., *et al.* Predictors of secondary surgery after hypospadias repair: a population based analysis of 5,000 patients. *J Urol*, 2013. 190: 251.
<https://www.ncbi.nlm.nih.gov/pubmed/23376710>
234. Braga, L.H., *et al.* Tubularized incised plate urethroplasty for distal hypospadias: A literature review. *Indian J Urol*, 2008. 24: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/19468401>

235. Wilkinson, D.J., *et al.* Outcomes in distal hypospadias: a systematic review of the Mathieu and tubularized incised plate repairs. *J Pediatr Urol*, 2012. 8: 307.
<https://www.ncbi.nlm.nih.gov/pubmed/21159560>
236. Wang, F., *et al.* Systematic review and meta-analysis of studies comparing the perimeatal-based flap and tubularized incised-plate techniques for primary hypospadias repair. *Pediatr Surg Int*, 2013. 29: 811.
<https://www.ncbi.nlm.nih.gov/pubmed/23793987>
237. Leslie, B., *et al.* Critical outcome analysis of staged buccal mucosa graft urethroplasty for prior failed hypospadias repair in children. *J Urol*, 2011. 185: 1077.
<https://www.ncbi.nlm.nih.gov/pubmed/21256520>
238. Spinoit, A.F., *et al.* Hypospadias repair at a tertiary care center: long-term followup is mandatory to determine the real complication rate. *J Urol*, 2013. 189: 2276.
<https://www.ncbi.nlm.nih.gov/pubmed/23306089>
239. Andersson, M., *et al.* Hypospadias repair with tubularized incised plate: Does the obstructive flow pattern resolve spontaneously? *J Pediatr Urol*, 2011. 7: 441.
<https://www.ncbi.nlm.nih.gov/pubmed/20630805>
240. Gonzalez, R., *et al.* Importance of urinary flow studies after hypospadias repair: a systematic review. *Int J Urol*, 2011. 18: 757.
<https://www.ncbi.nlm.nih.gov/pubmed/21883491>
241. Andersson, M., *et al.* Normalized Urinary Flow at Puberty after Tubularized Incised Plate Urethroplasty for Hypospadias in Childhood. *J Urol*, 2015. 194: 1407.
<https://www.ncbi.nlm.nih.gov/pubmed/26087380>
242. Hueber, P.A., *et al.* Long-term functional outcomes of distal hypospadias repair: a single center retrospective comparative study of TIPs, Mathieu and MAGPI. *J Pediatr Urol*, 2015. 11: 68 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/25824882>
243. Perera, M., *et al.* Long-term urethral function measured by uroflowmetry after hypospadias surgery: comparison with an age matched control. *J Urol*, 2012. 188: 1457.
<https://www.ncbi.nlm.nih.gov/pubmed/22906660>
244. Holland, A.J., *et al.* HOSE: an objective scoring system for evaluating the results of hypospadias surgery. *BJU Int*, 2001. 88: 255.
<https://www.ncbi.nlm.nih.gov/pubmed/11488741>
245. van der Toorn, F., *et al.* Introducing the HOPE (Hypospadias Objective Penile Evaluation)-score: a validation study of an objective scoring system for evaluating cosmetic appearance in hypospadias patients. *J Pediatr Urol*, 2013. 9: 1006.
<https://www.ncbi.nlm.nih.gov/pubmed/23491983>
246. Weber, D.M., *et al.* The Penile Perception Score: an instrument enabling evaluation by surgeons and patient self-assessment after hypospadias repair. *J Urol*, 2013. 189: 189.
<https://www.ncbi.nlm.nih.gov/pubmed/23174225>
247. Moriya, K., *et al.* Long-term cosmetic and sexual outcome of hypospadias surgery: norm related study in adolescence. *J Urol*, 2006. 176: 1889.
<https://www.ncbi.nlm.nih.gov/pubmed/16945681>
248. Rynja, S.P., *et al.* Functional, cosmetic and psychosexual results in adult men who underwent hypospadias correction in childhood. *J Pediatr Urol*, 2011. 7: 504.
<https://www.ncbi.nlm.nih.gov/pubmed/21429804>
249. Ortqvist, L., *et al.* Long-term followup of men born with hypospadias: urological and cosmetic results. *J Urol*, 2015. 193: 975.
<https://www.ncbi.nlm.nih.gov/pubmed/25268894>
250. Adams, J., *et al.* Reconstructive surgery for hypospadias: A systematic review of long-term patient satisfaction with cosmetic outcomes. *Indian J Urol*, 2016. 32: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/27127350>
251. Nyirady, P., *et al.* Management of congenital penile curvature. *J Urol*, 2008. 179: 1495.
<https://www.ncbi.nlm.nih.gov/pubmed/18295273>
252. Baskin, L.S., *et al.* Neuroanatomical ontogeny of the human fetal penis. *Br J Urol*, 1997. 79: 628.
<https://www.ncbi.nlm.nih.gov/pubmed/9126098>
253. Ebbelohj, J., *et al.* Congenital penile angulation. *Br J Urol*, 1987. 60: 264.
<https://www.ncbi.nlm.nih.gov/pubmed/3676675>
254. Kelami, A. Congenital penile deviation and its treatment with the Nesbit-Kelami technique. *Br J Urol*, 1987. 60: 261.
<https://www.ncbi.nlm.nih.gov/pubmed/3676674>

255. Yachia, D., *et al.* The incidence of congenital penile curvature. *J Urol*, 1993. 150: 1478.
<https://www.ncbi.nlm.nih.gov/pubmed/8411431>
256. Hsieh, J.T., *et al.* Correction of congenital penile curvature using modified tunical plication with absorbable sutures: the long-term outcome and patient satisfaction. *Eur Urol*, 2007. 52: 261.
<https://www.ncbi.nlm.nih.gov/pubmed/17234333>
257. Sasso, F., *et al.* Penile curvature: an update for management from 20 years experience in a high volume centre. *Urologia*, 2016. 83: 130.
<https://www.ncbi.nlm.nih.gov/pubmed/27103093>
258. Gittes, R.F., *et al.* Injection technique to induce penile erection. *Urology*, 1974. 4: 473.
<https://www.ncbi.nlm.nih.gov/pubmed/4418594>
259. Schultheiss, D., *et al.* Congenital and acquired penile deviation treated with the essed plication method. *Eur Urol*, 2000. 38: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/10895008>
260. Yachia, D. Modified corporoplasty for the treatment of penile curvature. *J Urol*, 1990. 143: 80.
<https://www.ncbi.nlm.nih.gov/pubmed/2294269>
261. Rehman, J., *et al.* Results of surgical treatment for abnormal penile curvature: Peyronie's disease and congenital deviation by modified Nesbit plication (tunica shaving and plication). *J Urol*, 1997. 157: 1288.
<https://www.ncbi.nlm.nih.gov/pubmed/9120923>
262. Poulsen, J., *et al.* Treatment of penile curvature--a retrospective study of 175 patients operated with plication of the tunica albuginea or with the Nesbit procedure. *Br J Urol*, 1995. 75: 370.
<https://www.ncbi.nlm.nih.gov/pubmed/7735803>
263. Leonardo, C., *et al.* Plication corporoplasty versus Nesbit operation for the correction of congenital penile curvature. A long-term follow-up. *Int Urol Nephrol*, 2012. 44: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/21559790>
264. Cavallini, G., *et al.* Pilot study to determine improvements in subjective penile morphology and personal relationships following a Nesbit plication procedure for men with congenital penile curvature. *Asian J Androl*, 2008. 10: 512.
<https://www.ncbi.nlm.nih.gov/pubmed/18097530>
265. Vatne, V., *et al.* Functional results after operations of penile deviations: an institutional experience. *Scand J Urol Nephrol Suppl*, 1996. 179: 151.
<https://www.ncbi.nlm.nih.gov/pubmed/8908683>
266. Shaeer, O., *et al.* Shaeer's Corporal Rotation III: Shortening-Free Correction of Congenital Penile Curvature-The Noncorporotomy Technique. *Eur Urol*, 2016. 69: 129.
<https://www.ncbi.nlm.nih.gov/pubmed/26298209>
267. Akbay, E., *et al.* The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. *BJU Int*, 2000. 86: 490.
<https://www.ncbi.nlm.nih.gov/pubmed/10971279>
268. Kogan, S.J., The pediatric varicocele. In: *Pediatric urology*, 2001, WB Saunders: Philadelphia.
269. Oster, J. Varicocele in children and adolescents. An investigation of the incidence among Danish school children. *Scand J Urol Nephrol*, 1971. 5: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/5093090>
270. Kass, E.J., *et al.* Reversal of testicular growth failure by varicocele ligation. *J Urol*, 1987. 137: 475.
<https://www.ncbi.nlm.nih.gov/pubmed/3820376>
271. Paduch, D.A., *et al.* Repair versus observation in adolescent varicocele: a prospective study. *J Urol*, 1997. 158: 1128.
<https://www.ncbi.nlm.nih.gov/pubmed/9258155>
272. Li, F., *et al.* Effect of varicolectomy on testicular volume in children and adolescents: a meta-analysis. *Urology*, 2012. 79: 1340.
<https://www.ncbi.nlm.nih.gov/pubmed/22516359>
273. Kocvara, R., *et al.* Division of lymphatic vessels at varicolectomy leads to testicular oedema and decline in testicular function according to the LH-RH analogue stimulation test. *Eur Urol*, 2003. 43: 430.
<https://www.ncbi.nlm.nih.gov/pubmed/12667726>
274. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. *World Health Organization. Fertil Steril*, 1992. 57: 1289.
<https://www.ncbi.nlm.nih.gov/pubmed/1601152>
275. Laven, J.S., *et al.* Effects of varicocele treatment in adolescents: a randomized study. *Fertil Steril*, 1992. 58: 756.
<https://www.ncbi.nlm.nih.gov/pubmed/1426322>

276. Okuyama, A., *et al.* Surgical repair of varicocele at puberty: preventive treatment for fertility improvement. *J Urol*, 1988. 139: 562.
<https://www.ncbi.nlm.nih.gov/pubmed/3343743>
277. Pinto, K.J., *et al.* Varicocele related testicular atrophy and its predictive effect upon fertility. *J Urol*, 1994. 152: 788.
<https://www.ncbi.nlm.nih.gov/pubmed/8022015>
278. Nork, J.J., *et al.* Youth varicocele and varicocele treatment: a meta-analysis of semen outcomes. *Fertil Steril*, 2014. 102: 381.
<https://www.ncbi.nlm.nih.gov/pubmed/24907913>
279. Dubin, L., *et al.* Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. *Fertil Steril*, 1970. 21: 606.
<https://www.ncbi.nlm.nih.gov/pubmed/5433164>
280. Tasci, A.I., *et al.* Color doppler ultrasonography and spectral analysis of venous flow in diagnosis of varicocele. *Eur Urol*, 2001. 39: 316.
<https://www.ncbi.nlm.nih.gov/pubmed/11275726>
281. Diamond, D.A., *et al.* Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents. *J Urol*, 2007. 178: 1584.
<https://www.ncbi.nlm.nih.gov/pubmed/17707046>
282. Aragona, F., *et al.* Correlation of testicular volume, histology and LHRH test in adolescents with idiopathic varicocele. *Eur Urol*, 1994. 26: 61.
<https://www.ncbi.nlm.nih.gov/pubmed/7925532>
283. Bogaert, G., *et al.* Pubertal screening and treatment for varicocele do not improve chance of paternity as adult. *J Urol*, 2013. 189: 2298.
<https://www.ncbi.nlm.nih.gov/pubmed/23261480>
284. Chen, J.J., *et al.* Is the comparison of a left varicocele testis to its contralateral normal testis sufficient in determining its well-being? *Urology*, 2011. 78: 1167.
<https://www.ncbi.nlm.nih.gov/pubmed/21782220>
285. Goldstein, M., *et al.* Microsurgical inguinal varicocelectomy with delivery of the testis: an artery and lymphatic sparing technique. *J Urol*, 1992. 148: 1808.
<https://www.ncbi.nlm.nih.gov/pubmed/1433614>
286. Hopps, C.V., *et al.* Intraoperative varicocele anatomy: a microscopic study of the inguinal versus subinguinal approach. *J Urol*, 2003. 170: 2366.
<https://www.ncbi.nlm.nih.gov/pubmed/14634418>
287. Kocvara, R., *et al.* Lymphatic sparing laparoscopic varicocelectomy: a microsurgical repair. *J Urol*, 2005. 173: 1751.
<https://www.ncbi.nlm.nih.gov/pubmed/15821575>
288. Riccabona, M., *et al.* Optimizing the operative treatment of boys with varicocele: sequential comparison of 4 techniques. *J Urol*, 2003. 169: 666.
<https://www.ncbi.nlm.nih.gov/pubmed/12544340>
289. Marmar, J., *et al.* New scientific information related to varicoceles. *J Urol*, 2003. 170: 2371.
<https://www.ncbi.nlm.nih.gov/pubmed/14634419>
290. Minevich, E., *et al.* Inguinal microsurgical varicocelectomy in the adolescent: technique and preliminary results. *J Urol*, 1998. 159: 1022.
<https://www.ncbi.nlm.nih.gov/pubmed/9474223>
291. Mirilas, P., *et al.* Microsurgical subinguinal varicocelectomy in children, adolescents, and adults: surgical anatomy and anatomically justified technique. *J Androl*, 2012. 33: 338.
<https://www.ncbi.nlm.nih.gov/pubmed/21835913>
292. Oswald, J., *et al.* The use of isosulphan blue to identify lymphatic vessels in high retroperitoneal ligation of adolescent varicocele--avoiding postoperative hydrocele. *BJU Int*, 2001. 87: 502.
<https://www.ncbi.nlm.nih.gov/pubmed/11298043>
293. Esposito, C., *et al.* Technical standardization of laparoscopic lymphatic sparing varicocelectomy in children using isosulfan blue. *J Pediatr Surg*, 2014. 49: 660.
<https://www.ncbi.nlm.nih.gov/pubmed/24726132>
294. Kim, K.S., *et al.* Impact of internal spermatic artery preservation during laparoscopic varicocelectomy on recurrence and the catch-up growth rate in adolescents. *J Pediatr Urol*, 2014. 10: 435.
<https://www.ncbi.nlm.nih.gov/pubmed/24314819>
295. Fast, A.M., *et al.* Adolescent varicocelectomy: does artery sparing influence recurrence rate and/or catch-up growth? *Andrology*, 2014. 2: 159.
<https://www.ncbi.nlm.nih.gov/pubmed/24339439>

296. Fayad, F., *et al.* Percutaneous retrograde endovascular occlusion for pediatric varicocele. *J Pediatr Surg*, 2011. 46: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/21376204>
297. Thon, W.F., *et al.* Percutaneous sclerotherapy of idiopathic varicocele in childhood: a preliminary report. *J Urol*, 1989. 141: 913.
<https://www.ncbi.nlm.nih.gov/pubmed/2926889>
298. Hoberman, A., *et al.* Prevalence of urinary tract infection in febrile infants. *J Pediatr*, 1993. 123: 17.
<https://www.ncbi.nlm.nih.gov/pubmed/8320616>
299. Marild, S., *et al.* Incidence rate of first-time symptomatic urinary tract infection in children under 6 years of age. *Acta Paediatr*, 1998. 87: 549.
<https://www.ncbi.nlm.nih.gov/pubmed/9641738>
300. O'Brien, K., *et al.* Prevalence of urinary tract infection (UTI) in sequential acutely unwell children presenting in primary care: exploratory study. *Scand J Prim Health Care*, 2011. 29: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/21323495>
301. Kunin, C.M., *et al.* Sensitivity of a nitrite indicator strip method in detecting bacteriuria in preschool girls. *Pediatrics*, 1977. 60: 244.
<https://www.ncbi.nlm.nih.gov/pubmed/887340>
302. Shaikh, N., *et al.* Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatr Infect Dis J*, 2008. 27: 302.
<https://www.ncbi.nlm.nih.gov/pubmed/18316994>
303. Winberg, J., *et al.* Epidemiology of symptomatic urinary tract infection in childhood. *Acta Paediatr Scand Suppl*, 1974: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/4618418>
304. Zorc, J.J., *et al.* Clinical and demographic factors associated with urinary tract infection in young febrile infants. *Pediatrics*, 2005. 116: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/16140703>
305. Rushton, H.G., *et al.* Pyelonephritis in male infants: how important is the foreskin? *J Urol*, 1992. 148: 733.
<https://www.ncbi.nlm.nih.gov/pubmed/1640557>
306. Magin, E.C., *et al.* Efficacy of short-term intravenous antibiotic in neonates with urinary tract infection. *Pediatr Emerg Care*, 2007. 23: 83.
<https://www.ncbi.nlm.nih.gov/pubmed/17351406>
307. Sastre, J.B., *et al.* Urinary tract infection in the newborn: clinical and radio imaging studies. *Pediatr Nephrol*, 2007. 22: 1735.
<https://www.ncbi.nlm.nih.gov/pubmed/17665222>
308. Shortliffe, L.M.D., *et al.*, Pediatric urinary tract infections. in *Pediatric Urology*, 2001, Saunders: Philadelphia.
309. Burns, M.W., *et al.* Pediatric urinary tract infection. Diagnosis, classification, and significance. *Pediatr Clin North Am*, 1987. 34: 1111.
<https://www.ncbi.nlm.nih.gov/pubmed/3658502>
310. Beetz, R., *et al.* [Urinary tract infections in infants and children -- a consensus on diagnostic, therapy and prophylaxis]. *Urologe A*, 2007. 46: 112.
<https://www.ncbi.nlm.nih.gov/pubmed/17225140>
311. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. *Pediatrics*, 1999. 103: 843.
<https://www.ncbi.nlm.nih.gov/pubmed/10103321>
312. Craig, J.C., *et al.* The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses. *Bmj*, 2010. 340: c1594.
<https://www.ncbi.nlm.nih.gov/pubmed/20406860>
313. Lin, D.S., *et al.* Urinary tract infection in febrile infants younger than eight weeks of Age. *Pediatrics*, 2000. 105: E20.
<https://www.ncbi.nlm.nih.gov/pubmed/10654980>
314. Tullus, K. Difficulties in diagnosing urinary tract infections in small children. *Pediatr Nephrol*, 2011. 26: 1923.
<https://www.ncbi.nlm.nih.gov/pubmed/21773821>
315. Whiting, P., *et al.* Rapid tests and urine sampling techniques for the diagnosis of urinary tract infection (UTI) in children under five years: a systematic review. *BMC Pediatr*, 2005. 5: 4.
<https://www.ncbi.nlm.nih.gov/pubmed/15811182>

316. Koch, V.H., *et al.* [Urinary tract infection: a search for evidence]. *J Pediatr (Rio J)*, 2003. 79 Suppl 1: S97.
<https://www.ncbi.nlm.nih.gov/pubmed/14506522>
317. Ma, J.F., *et al.* Urinary tract infection in children: etiology and epidemiology. *Urol Clin North Am*, 2004. 31: 517.
<https://www.ncbi.nlm.nih.gov/pubmed/15313061>
318. Ramage, I.J., *et al.* Accuracy of clean-catch urine collection in infancy. *J Pediatr*, 1999. 135: 765.
<https://www.ncbi.nlm.nih.gov/pubmed/10586183>
319. Roberts, K.B., *et al.* Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*, 2011. 128: 595.
<https://www.ncbi.nlm.nih.gov/pubmed/21873693>
320. Tosif, S., *et al.* Contamination rates of different urine collection methods for the diagnosis of urinary tract infections in young children: an observational cohort study. *J Paediatr Child Health*, 2012. 48: 659.
<https://www.ncbi.nlm.nih.gov/pubmed/22537082>
321. Austin, B.J., *et al.* Is urethral catheterization a successful alternative to suprapubic aspiration in neonates? *J Paediatr Child Health*, 1999. 35: 34.
<https://www.ncbi.nlm.nih.gov/pubmed/10234632>
322. Wingerter, S., *et al.* Risk factors for contamination of catheterized urine specimens in febrile children. *Pediatr Emerg Care*, 2011. 27: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/21178815>
323. Buys, H., *et al.* Suprapubic aspiration under ultrasound guidance in children with fever of undiagnosed cause. *Bmj*, 1994. 308: 690.
<https://www.ncbi.nlm.nih.gov/pubmed/8142792>
324. Kiernan, S.C., *et al.* Ultrasound guidance of suprapubic bladder aspiration in neonates. *J Pediatr*, 1993. 123: 789.
<https://www.ncbi.nlm.nih.gov/pubmed/8142792>
325. Hildebrand, W.L., *et al.* Suprapubic bladder aspiration in infants. *Am Fam Physician*, 1981. 23: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/7234629>
326. Kozar, E., *et al.* Pain in infants who are younger than 2 months during suprapubic aspiration and transurethral bladder catheterization: a randomized, controlled study. *Pediatrics*, 2006. 118: e51.
<https://www.ncbi.nlm.nih.gov/pubmed/16818537>
327. Vaillancourt, S., *et al.* To clean or not to clean: effect on contamination rates in midstream urine collections in toilet-trained children. *Pediatrics*, 2007. 119: e1288.
<https://www.ncbi.nlm.nih.gov/pubmed/17502345>
328. Powell, H.R., *et al.* Urinary nitrite in symptomatic and asymptomatic urinary infection. *Arch Dis Child*, 1987. 62: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/3548604>
329. Stull, T.L., *et al.* Epidemiology and natural history of urinary tract infections in children. *Med Clin North Am*, 1991. 75: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/1996034>
330. Hoberman, A., *et al.* Is urine culture necessary to rule out urinary tract infection in young febrile children? *Pediatr Infect Dis J*, 1996. 15: 304.
<https://www.ncbi.nlm.nih.gov/pubmed/8866798>
331. Herr, S.M., *et al.* Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. *Pediatrics*, 2001. 108: 866.
<https://www.ncbi.nlm.nih.gov/pubmed/11581437>
332. Mayo, S., *et al.* Clinical laboratory automated urinalysis: comparison among automated microscopy, flow cytometry, two test strips analyzers, and manual microscopic examination of the urine sediments. *J Clin Lab Anal*, 2008. 22: 262.
<https://www.ncbi.nlm.nih.gov/pubmed/18623125>
333. Kass, E.H. Asymptomatic infections of the urinary tract. *Trans Assoc Am Physicians*, 1956. 69: 56.
<https://www.ncbi.nlm.nih.gov/pubmed/13380946>
334. Lohr, J.A. Use of routine urinalysis in making a presumptive diagnosis of urinary tract infection in children. *Pediatr Infect Dis J*, 1991. 10: 646.
<https://www.ncbi.nlm.nih.gov/pubmed/1923675>
335. Bollgren, I., *et al.* Low urinary counts of P-fimbriated *Escherichia coli* in presumed acute pyelonephritis. *Arch Dis Child*, 1984. 59: 102.
<https://www.ncbi.nlm.nih.gov/pubmed/6142697>

336. Stamm, W.E. Measurement of pyuria and its relation to bacteriuria. *Am J Med*, 1983. 75: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/6349345>
337. Grabe, M., *et al.*, EAU Guidelines on Urological Infections. Presented at the EAU Annual Congress, ed. European Association of Urology. 2011, Arnhem, The Netherlands
338. Preda, I., *et al.* Value of ultrasound in evaluation of infants with first urinary tract infection. *J Urol*, 2010. 183: 1984.
<https://www.ncbi.nlm.nih.gov/pubmed/20303537>
339. Chang, S.J., *et al.* Elevated postvoid residual urine volume predicting recurrence of urinary tract infections in toilet-trained children. *Pediatr Nephrol*, 2015. 30: 1131.
<https://www.ncbi.nlm.nih.gov/pubmed/25673516>
340. Shiraishi, K., *et al.* Risk factors for breakthrough infection in children with primary vesicoureteral reflux. *J Urol*, 2010. 183: 1527.
<https://www.ncbi.nlm.nih.gov/pubmed/20172558>
341. Quirino, I.G., *et al.* Combined use of late phase dimercapto-succinic acid renal scintigraphy and ultrasound as first line screening after urinary tract infection in children. *J Urol*, 2011. 185: 258.
<https://www.ncbi.nlm.nih.gov/pubmed/21074813>
342. Siomou, E., *et al.* Implications of 99mTc-DMSA scintigraphy performed during urinary tract infection in neonates. *Pediatrics*, 2009. 124: 881.
<https://www.ncbi.nlm.nih.gov/pubmed/19661052>
343. Doganis, D., *et al.* Timing of voiding cystourethrography in infants with first time urinary infection. *Pediatr Nephrol*, 2009. 24: 319.
<https://www.ncbi.nlm.nih.gov/pubmed/18853200>
344. Sathapornwajana, P., *et al.* Timing of voiding cystourethrogram after urinary tract infection. *Arch Dis Child*, 2008. 93: 229.
<https://www.ncbi.nlm.nih.gov/pubmed/17626141>
345. Spencer, J.D., *et al.* The accuracy and health risks of a voiding cystourethrogram after a febrile urinary tract infection. *J Pediatr Urol*, 2012. 8: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/21126919>
346. Hoebeke, P., *et al.* Assessment of lower urinary tract dysfunction in children with non-neuropathic bladder sphincter dysfunction. *Eur Urol*, 1999. 35: 57.
<https://www.ncbi.nlm.nih.gov/pubmed/9933796>
347. Koff, S.A., *et al.* The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. *J Urol*, 1998. 160: 1019.
<https://www.ncbi.nlm.nih.gov/pubmed/9719268>
348. van Gool, J.D. Dysfunctional voiding: a complex of bladder/sphincter dysfunction, urinary tract infections and vesicoureteral reflux. *Acta Urol Belg*, 1995. 63: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/7484519>
349. van Gool, J.D., *et al.* Bladder-sphincter dysfunction, urinary infection and vesico-ureteral reflux with special reference to cognitive bladder training. *Contrib Nephrol*, 1984. 39: 190.
<https://www.ncbi.nlm.nih.gov/pubmed/6744871>
350. De Paepe, H., *et al.* Pelvic-floor therapy and toilet training in young children with dysfunctional voiding and obstipation. *BJU Int*, 2000. 85: 889.
<https://www.ncbi.nlm.nih.gov/pubmed/10792172>
351. Loening-Baucke, V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. *Pediatrics*, 1997. 100: 228.
<https://www.ncbi.nlm.nih.gov/pubmed/9240804>
352. O'Regan, S., *et al.* Constipation, bladder instability, urinary tract infection syndrome. *Clin Nephrol*, 1985. 23: 152.
<https://www.ncbi.nlm.nih.gov/pubmed/3987104>
353. Tutunculer, F., *et al.* Transient Pseudohypoaldosteronism in an infant with urinary tract anomaly. *Pediatr Int*, 2004. 46: 618.
<https://www.ncbi.nlm.nih.gov/pubmed/15491397>
354. Nandagopal, R., *et al.* Transient Pseudohypoaldosteronism due to Urinary Tract Infection in Infancy: A Report of 4 Cases. *Int J Pediatr Endocrinol*, 2009. 2009: 195728.
<https://www.ncbi.nlm.nih.gov/pubmed/19946403>
355. Contopoulos-Ioannidis, D.G., *et al.* Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics*, 2004. 114: e111.
<https://www.ncbi.nlm.nih.gov/pubmed/15231982>

356. Hodson, E.M., *et al.* Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev*, 2007: CD003772.
<https://www.ncbi.nlm.nih.gov/pubmed/17943796>
357. Dore-Bergeron, M.J., *et al.* Urinary tract infections in 1- to 3-month-old infants: ambulatory treatment with intravenous antibiotics. *Pediatrics*, 2009. 124: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/19564278>
358. Gauthier, M., *et al.* Treatment of urinary tract infections among febrile young children with daily intravenous antibiotic therapy at a day treatment center. *Pediatrics*, 2004. 114: e469.
<https://www.ncbi.nlm.nih.gov/pubmed/15466073>
359. Bouissou, F., *et al.* Prospective, randomized trial comparing short and long intravenous antibiotic treatment of acute pyelonephritis in children: dimercaptosuccinic acid scintigraphic evaluation at 9 months. *Pediatrics*, 2008. 121: e553.
<https://www.ncbi.nlm.nih.gov/pubmed/18267977>
360. Craig, J.C., *et al.* Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med*, 2009. 361: 1748.
<https://www.ncbi.nlm.nih.gov/pubmed/19864673>
361. Hoberman, A., *et al.* Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics*, 1999. 104: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/10390264>
362. Neuhaus, T.J., *et al.* Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis. *Eur J Pediatr*, 2008. 167: 1037.
<https://www.ncbi.nlm.nih.gov/pubmed/18074149>
363. Montini, G., *et al.* Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. *Bmj*, 2007. 335: 386.
<https://www.ncbi.nlm.nih.gov/pubmed/17611232>
364. Mak, R.H., *et al.* Are oral antibiotics alone efficacious for the treatment of a first episode of acute pyelonephritis in children? *Nat Clin Pract Nephrol*, 2008. 4: 10.
<https://www.ncbi.nlm.nih.gov/pubmed/17971799>
365. Klar, A., *et al.* Focal bacterial nephritis (lobar nephronia) in children. *J Pediatr*, 1996. 128: 850.
<https://www.ncbi.nlm.nih.gov/pubmed/8648547>
366. Cheng, C.H., *et al.* Effective duration of antimicrobial therapy for the treatment of acute lobar nephronia. *Pediatrics*, 2006. 117: e84.
<https://www.ncbi.nlm.nih.gov/pubmed/16326693>
367. Ramos, N.L., *et al.* Characterisation of uropathogenic *Escherichia coli* from children with urinary tract infection in different countries. *Eur J Clin Microbiol Infect Dis*, 2011. 30: 1587.
<https://www.ncbi.nlm.nih.gov/pubmed/21509475>
368. Kizilca, O., *et al.* Risk factors for community-acquired urinary tract infection caused by ESBL-producing bacteria in children. *Pediatr Int*, 2012. 54: 858.
<https://www.ncbi.nlm.nih.gov/pubmed/22882781>
369. Tratselas, A., *et al.* Outcome of urinary tract infections caused by extended spectrum beta-lactamase-producing Enterobacteriaceae in children. *Pediatr Infect Dis J*, 2011. 30: 707.
<https://www.ncbi.nlm.nih.gov/pubmed/21248655>
370. Naber, K.G., *et al.*, EAU/International Consultation on Urological Infections 2010, European Association of Urology: The Netherlands.
371. Montini, G., *et al.* Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics*, 2008. 122: 1064.
<https://www.ncbi.nlm.nih.gov/pubmed/18977988>
372. Garin, E.H., *et al.* Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics*, 2006. 117: 626.
<https://www.ncbi.nlm.nih.gov/pubmed/16510640>
373. Pennesi, M., *et al.* Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics*, 2008. 121: e1489.
<https://www.ncbi.nlm.nih.gov/pubmed/18490378>
374. Roussey-Kesler, G., *et al.* Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. *J Urol*, 2008. 179: 674.
<https://www.ncbi.nlm.nih.gov/pubmed/18082208>

375. Hari, P., *et al.* Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*, 2014. 371: 1071.
<https://www.ncbi.nlm.nih.gov/pubmed/25207775>
376. Wang, H.H., *et al.* Efficacy of antibiotic prophylaxis in children with vesicoureteral reflux: systematic review and meta-analysis. *J Urol*, 2015. 193: 963.
<https://www.ncbi.nlm.nih.gov/pubmed/25196653>
377. Lee, S.J., *et al.* Probiotics prophylaxis in infants with primary vesicoureteral reflux. *Pediatr Nephrol*, 2015. 30: 609.
<https://www.ncbi.nlm.nih.gov/pubmed/25354903>
378. Salo, J., *et al.* Cranberry juice for the prevention of recurrences of urinary tract infections in children: a randomized placebo-controlled trial. *Clin Infect Dis*, 2012. 54: 340.
<https://www.ncbi.nlm.nih.gov/pubmed/22100577>
379. Afshar, K., *et al.* Cranberry juice for the prevention of pediatric urinary tract infection: a randomized controlled trial. *J Urol*, 2012. 188: 1584.
<https://www.ncbi.nlm.nih.gov/pubmed/22910239>
380. Schwenger, E.M., *et al.* Probiotics for preventing urinary tract infections in adults and children. *Cochrane Database Syst Rev*, 2015: CD008772.
<https://www.ncbi.nlm.nih.gov/pubmed/26695595>
381. Kotoula, A., *et al.* Comparative efficacies of procalcitonin and conventional inflammatory markers for prediction of renal parenchymal inflammation in pediatric first urinary tract infection. *Urology*, 2009. 73: 782.
<https://www.ncbi.nlm.nih.gov/pubmed/19152962>
382. Austin, P.F., *et al.* The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. *Neurourol Urodyn*, 2016. 35: 471.
<https://www.ncbi.nlm.nih.gov/pubmed/25772695>
383. Hellstrom, A.L., *et al.* Micturition habits and incontinence in 7-year-old Swedish school entrants. *Eur J Pediatr*, 1990. 149: 434.
<https://www.ncbi.nlm.nih.gov/pubmed/2332015>
384. Bakker, E., *et al.* Voiding habits and wetting in a population of 4,332 Belgian schoolchildren aged between 10 and 14 years. *Scand J Urol Nephrol*, 2002. 36: 354.
<https://www.ncbi.nlm.nih.gov/pubmed/12487740>
385. Soderstrom, U., *et al.* Urinary and faecal incontinence: a population-based study. *Acta Paediatr*, 2004. 93: 386.
<https://www.ncbi.nlm.nih.gov/pubmed/15124844>
386. Sureshkumar, P., *et al.* Daytime urinary incontinence in primary school children: a population-based survey. *J Pediatr*, 2000. 137: 814.
<https://www.ncbi.nlm.nih.gov/pubmed/11113838>
387. Sureshkumar, P., *et al.* A population based study of 2,856 school-age children with urinary incontinence. *J Urol*, 2009. 181: 808.
<https://www.ncbi.nlm.nih.gov/pubmed/19110268>
388. Veiga, M.L., *et al.* Constipation in children with isolated overactive bladders. *J Pediatr Urol*, 2013. 9: 945.
<https://www.ncbi.nlm.nih.gov/pubmed/23462384>
389. Borch, L., *et al.* Bladder and bowel dysfunction and the resolution of urinary incontinence with successful management of bowel symptoms in children. *Acta Paediatr*, 2013. 102: e215.
<https://www.ncbi.nlm.nih.gov/pubmed/23368903>
390. Chang, S.J., *et al.* Treatment of daytime urinary incontinence: A standardization document from the International Children's Continence Society. *Neurourol Urodyn*, 2015.
<https://www.ncbi.nlm.nih.gov/pubmed/26473630>
391. Hoebeke, P., *et al.* Diagnostic evaluation of children with daytime incontinence. *J Urol*, 2010. 183: 699.
<https://www.ncbi.nlm.nih.gov/pubmed/20022025>
392. Akbal, C., *et al.* Dysfunctional voiding and incontinence scoring system: quantitative evaluation of incontinence symptoms in pediatric population. *J Urol*, 2005. 173: 969.
<https://www.ncbi.nlm.nih.gov/pubmed/15711352>
393. Farhat, W., *et al.* The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. *J Urol*, 2000. 164: 1011.
<https://www.ncbi.nlm.nih.gov/pubmed/10958730>

394. Chang, S.J., *et al.* Constipation is associated with incomplete bladder emptying in healthy children. *Neurourol Urodyn*, 2012. 31: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/22038844>
395. Burgers, R.E., *et al.* Management of functional constipation in children with lower urinary tract symptoms: report from the Standardization Committee of the International Children's Continence Society. *J Urol*, 2013. 190: 29.
<https://www.ncbi.nlm.nih.gov/pubmed/23313210>
396. van Gool, J.D., *et al.* Multi-center randomized controlled trial of cognitive treatment, placebo, oxybutynin, bladder training, and pelvic floor training in children with functional urinary incontinence. *Neurourol Urodyn*, 2014. 33: 482.
<https://www.ncbi.nlm.nih.gov/pubmed/23775924>
397. Hellstrom, A.L. Urotherapy in children with dysfunctional bladder. *Scand J Urol Nephrol Suppl*, 1992. 141: 106.
<https://www.ncbi.nlm.nih.gov/pubmed/1609245>
398. Barroso, U., Jr., *et al.* Electrical stimulation for lower urinary tract dysfunction in children: a systematic review of the literature. *Neurourol Urodyn*, 2011. 30: 1429.
<https://www.ncbi.nlm.nih.gov/pubmed/21717502>
399. Bower, W.F., *et al.* A review of non-invasive electro neuromodulation as an intervention for non-neurogenic bladder dysfunction in children. *Neurourol Urodyn*, 2004. 23: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/14694460>
400. De Paepe, H., *et al.* Pelvic-floor therapy in girls with recurrent urinary tract infections and dysfunctional voiding. *Br J Urol*, 1998. 81 Suppl 3: 109.
<https://www.ncbi.nlm.nih.gov/pubmed/10792172>
401. Vijverberg, M.A., *et al.* Bladder rehabilitation, the effect of a cognitive training programme on urge incontinence. *Eur Urol*, 1997. 31: 68.
<https://www.ncbi.nlm.nih.gov/pubmed/9032538>
402. Lordelo, P., *et al.* Prospective study of transcutaneous parasacral electrical stimulation for overactive bladder in children: long-term results. *J Urol*, 2009. 182: 2900.
<https://www.ncbi.nlm.nih.gov/pubmed/19846164>
403. Ladi-Seyedian, S., *et al.* Management of non-neuropathic underactive bladder in children with voiding dysfunction by animated biofeedback: a randomized clinical trial. *Urology*, 2015. 85: 205.
<https://www.ncbi.nlm.nih.gov/pubmed/25444633>
404. Kajbafzadeh, A.M., *et al.* Transcutaneous interferential electrical stimulation for the management of non-neuropathic underactive bladder in children: a randomised clinical trial. *BJU Int*, 2016. 117: 793.
<https://www.ncbi.nlm.nih.gov/pubmed/26086897>
405. Featherstone, N., *et al.* Ephedrine hydrochloride: novel use in the management of resistant non-neurogenic daytime urinary incontinence in children. *J Pediatr Urol*, 2013. 9: 915.
<https://www.ncbi.nlm.nih.gov/pubmed/23332206>
406. Nijman, R.J., *et al.* Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. *J Urol*, 2005. 173: 1334.
<https://www.ncbi.nlm.nih.gov/pubmed/15758796>
407. Marschall-Kehrel, D., *et al.* Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial. *Eur Urol*, 2009. 55: 729.
<https://www.ncbi.nlm.nih.gov/pubmed/18502028>
408. Kramer, S.A., *et al.* Double-blind placebo controlled study of alpha-adrenergic receptor antagonists (doxazosin) for treatment of voiding dysfunction in the pediatric population. *J Urol*, 2005. 173: 2121.
<https://www.ncbi.nlm.nih.gov/pubmed/15879863>
409. Hoebeke, P., *et al.* The effect of botulinum-A toxin in incontinent children with therapy resistant overactive detrusor. *J Urol*, 2006. 176: 328.
<https://www.ncbi.nlm.nih.gov/pubmed/16753434>
410. Groen, L.A., *et al.* Sacral neuromodulation with an implantable pulse generator in children with lower urinary tract symptoms: 15-year experience. *J Urol*, 2012. 188: 1313.
<https://www.ncbi.nlm.nih.gov/pubmed/22902022>
411. Lackgren, G., *et al.* Nocturnal enuresis: a suggestion for a European treatment strategy. *Acta Paediatr*, 1999. 88: 679.
<https://www.ncbi.nlm.nih.gov/pubmed/10419258>

412. Neveus, T., *et al.* The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. *J Urol*, 2006. 176: 314.
<https://www.ncbi.nlm.nih.gov/pubmed/16753432>
413. Neveus, T., *et al.* Enuresis--background and treatment. *Scand J Urol Nephrol Suppl*, 2000: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/11196246>
414. Negoro, H., *et al.* Chronobiology of micturition: putative role of the circadian clock. *J Urol*, 2013. 190: 843.
<https://www.ncbi.nlm.nih.gov/pubmed/23429068>
415. Hjalmas, K., *et al.* Nocturnal enuresis: an international evidence based management strategy. *J Urol*, 2004. 171: 2545.
<https://www.ncbi.nlm.nih.gov/pubmed/10419258>
416. Caldwell, P.H., *et al.* Simple behavioural interventions for nocturnal enuresis in children. *Cochrane Database Syst Rev*, 2013. 7: CD003637.
<https://www.ncbi.nlm.nih.gov/pubmed/23881652>
417. Glazener, C.M., *et al.* Alarm interventions for nocturnal enuresis in children. *Cochrane Database Syst Rev*, 2005: CD002911.
<https://www.ncbi.nlm.nih.gov/pubmed/15846643>
418. Dehoorne, J.L., *et al.* Desmopressin toxicity due to prolonged half-life in 18 patients with nocturnal enuresis. *J Urol*, 2006. 176: 754.
<https://www.ncbi.nlm.nih.gov/pubmed/16813936>
419. Glazener, C.M., *et al.* Desmopressin for nocturnal enuresis in children. *Cochrane Database Syst Rev*, 2002: CD002112.
<https://www.ncbi.nlm.nih.gov/pubmed/12137645>
420. Gokce, M.I., *et al.* Does structured withdrawal of desmopressin improve relapse rates in patients with monosymptomatic enuresis? *J Urol*, 2014. 192: 530.
<https://www.ncbi.nlm.nih.gov/pubmed/24518770>
421. Glazener, C.M., *et al.* Tricyclic and related drugs for nocturnal enuresis in children. *Cochrane Database Syst Rev*, 2003: CD002117.
<https://www.ncbi.nlm.nih.gov/pubmed/12917922>
422. Bauer, S.B. The management of the myelodysplastic child: a paradigm shift. *BJU Int*, 2003. 92 Suppl 1: 23.
<https://www.ncbi.nlm.nih.gov/pubmed/>
423. Lapedes, J., *et al.* Clean, intermittent self-catheterization in the treatment of urinary tract disease. 1972. *J Urol*, 2002. 167: 1131.
<https://www.ncbi.nlm.nih.gov/pubmed/>
424. Retik, A.B., *et al.* Cutaneous ureteroileostomy in children. *N Engl J Med*, 1967. 277: 217.
<https://www.ncbi.nlm.nih.gov/pubmed/>
425. Bauer, S.B., The management of spina bifida from birth onwards., in *Paediatric urology*, R.H. Whitaker & J.R. Woodard, Eds. 1985, Butterworths: London.
426. Bauer, S.B., Early evaluation and management of children with spina bifida., in *Urologic surgery in neonates and young infants.*, L.R. King, Editor. 1988, WB Saunders: Philadelphia.
427. Hunt, G.M., *et al.* The pattern of congenital renal anomalies associated with neural-tube defects. *Dev Med Child Neurol*, 1987. 29: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/3556803>
428. Wilcock, A.R., *et al.* Deformities of the renal tract in children with meningomyelocele and hydrocephalus, compared with those of children showing no such central nervous system deformities. *Br J Urol*, 1970. 42: 152.
<https://www.ncbi.nlm.nih.gov/pubmed/5420153>
429. Pierre-Kahn, A., *et al.* Congenital lumbosacral lipomas. *Childs Nerv Syst*, 1997. 13: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/9272285>
430. Aoki, H., *et al.* [Evaluation of neurogenic bladder in patients with spinal cord injury using a CMG. EMG study and CMG.UFM.EMG study]. *Hinyokika Kyo*, 1985. 31: 937.
<https://www.ncbi.nlm.nih.gov/pubmed/4061211>
431. Bradley, C.S., *et al.* Urodynamic evaluation of the bladder and pelvic floor. *Gastroenterol Clin North Am*, 2008. 37: 539.
<https://www.ncbi.nlm.nih.gov/pubmed/18793995>
432. Casado, J.S., *et al.* [Urodynamic assessment of the voiding phase in childhood]. *Arch Esp Urol*, 2002. 55: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/12014050>

433. Wen, J.G., *et al.* Cystometry techniques in female infants and children. *Int Urogynecol J Pelvic Floor Dysfunct*, 2000. 11: 103.
<https://www.ncbi.nlm.nih.gov/pubmed/10805268>
434. Norgaard, J.P., *et al.* Standardization and definitions in lower urinary tract dysfunction in children. *International Children's Continence Society. Br J Urol*, 1998. 81 Suppl 3: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/9634012>
435. Agarwal, S.K., *et al.* Urodynamic correlates of resolution of reflux in meningomyelocele patients. *J Urol*, 1997. 158: 580.
<https://www.ncbi.nlm.nih.gov/pubmed/9224367>
436. Ghoniem, G.M., *et al.* The value of leak pressure and bladder compliance in the urodynamic evaluation of meningomyelocele patients. *J Urol*, 1990. 144: 1440.
<https://www.ncbi.nlm.nih.gov/pubmed/2231938>
437. Ghoniem, G.M., *et al.* Detrusor properties in myelomeningocele patients: in vitro study. *J Urol*, 1998. 159: 2193.
<https://www.ncbi.nlm.nih.gov/pubmed/9598568>
438. Palmer, L.S., *et al.* Age related bladder capacity and bladder capacity growth in children with myelomeningocele. *J Urol*, 1997. 158: 1261.
<https://www.ncbi.nlm.nih.gov/pubmed/9258190>
439. Tanikaze, S., *et al.* [Cystometric examination for neurogenic bladder of neonates and infants]. *Hinyokika Kyo*, 1991. 37: 1403.
<https://www.ncbi.nlm.nih.gov/pubmed/1767767>
440. Zoller, G., *et al.* Pre- and postoperative urodynamic findings in children with tethered spinal cord syndrome. *Eur Urol*, 1991. 19: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/2022217>
441. Webb, R.J., *et al.* Measurement of voiding pressures on ambulatory monitoring: comparison with conventional cystometry. *Br J Urol*, 1990. 65: 152.
<https://www.ncbi.nlm.nih.gov/pubmed/2317646>
442. Zermann, D.H., *et al.* Diagnostic value of natural fill cystometry in neurogenic bladder in children. *Eur Urol*, 1997. 32: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/9286658>
443. McInerney, P.D., *et al.* Ambulatory urodynamics. *Br J Urol*, 1991. 67: 272.
<https://www.ncbi.nlm.nih.gov/pubmed/2021814>
444. Yeung, C.K., *et al.* Natural filling cystometry in infants and children. *Br J Urol*, 1995. 75: 531.
<https://www.ncbi.nlm.nih.gov/pubmed/7788266>
445. Swithinbank, L.V., *et al.* Role of ambulatory urodynamic monitoring in clinical urological practice. *Neurourol Urodyn*, 1999. 18: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/10338442>
446. Rodriguez-Ruiz, M., *et al.* Study of kidney damage in paediatric patients with neurogenic bladder and its relationship with the pattern of bladder function and treatment received. *Actas Urol Esp*, 2016. 40: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/26183019>
447. McGuire, E.J., *et al.* Prognostic value of urodynamic testing in myelodysplastic patients. 1981. *J Urol*, 2002. 167: 1049.
<https://www.ncbi.nlm.nih.gov/pubmed/11905876>
448. Sillen, U., *et al.* Development of the urodynamic pattern in infants with myelomeningocele. *Br J Urol*, 1996. 78: 596.
<https://www.ncbi.nlm.nih.gov/pubmed/8944517>
449. Tarcan, T., *et al.* Long-term followup of newborns with myelodysplasia and normal urodynamic findings: Is followup necessary? *J Urol*, 2001. 165: 564.
<https://www.ncbi.nlm.nih.gov/pubmed/11176436>
450. Bauer, S.B. The argument for early assessment and treatment of infants with spina bifida *Dialogues Pediatr Urol* 2000. 23: 2.
451. Kaefer, M., *et al.* Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomeningocele. *J Urol*, 1999. 162: 1068.
<https://www.ncbi.nlm.nih.gov/pubmed/10458433>
452. Kasabian, N.G., *et al.* The prophylactic value of clean intermittent catheterization and anticholinergic medication in newborns and infants with myelodysplasia at risk of developing urinary tract deterioration. *Am J Dis Child*, 1992. 146: 840.
<https://www.ncbi.nlm.nih.gov/pubmed/1496955>

453. Kaufman, A.M., *et al.* Decreased bladder compliance in patients with myelomeningocele treated with radiological observation. *J Urol*, 1996. 156: 2031.
<https://www.ncbi.nlm.nih.gov/pubmed/8965337>
454. Lin-Dyken, D.C., *et al.* Follow-up of clean intermittent catheterization for children with neurogenic bladders. *Urology*, 1992. 40: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/1466106>
455. Wang, S.C., *et al.* Urethral dilation in the management of urological complications of myelodysplasia. *J Urol*, 1989. 142: 1054.
<https://www.ncbi.nlm.nih.gov/pubmed/2795730>
456. Wu, H.Y., *et al.* Neurogenic bladder dysfunction due to myelomeningocele: neonatal versus childhood treatment. *J Urol*, 1997. 157: 2295.
<https://www.ncbi.nlm.nih.gov/pubmed/9146656>
457. Park, J.M. Early reduction of mechanical load of the bladder improves compliance: experimental and clinical observations. *Dialogues Pediatr Urol* 2000. 23: 6.
458. Joseph, D.B., *et al.* Clean, intermittent catheterization of infants with neurogenic bladder. *Pediatrics*, 1989. 84: 78.
<https://www.ncbi.nlm.nih.gov/pubmed/2740179>
459. Lindehall, B., *et al.* Long-term intermittent catheterization: the experience of teenagers and young adults with myelomeningocele. *J Urol*, 1994. 152: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/8201663>
460. Baskin, L.S., *et al.* Treatment of infants with neurogenic bladder dysfunction using anticholinergic drugs and intermittent catheterisation. *Br J Urol*, 1990. 66: 532.
<https://www.ncbi.nlm.nih.gov/pubmed/2249125>
461. Connor, J.P., *et al.* Early cystometrograms can predict the response to intravesical instillation of oxybutynin chloride in myelomeningocele patients. *J Urol*, 1994. 151: 1045.
<https://www.ncbi.nlm.nih.gov/pubmed/8126787>
462. Ellsworth, P.I., *et al.* Use of tolterodine in children with neurogenic detrusor overactivity: relationship between dose and urodynamic response. *J Urol*, 2005. 174: 1647.
<https://www.ncbi.nlm.nih.gov/pubmed/16148673>
463. Ferrara, P., *et al.* Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida. *BJU Int*, 2001. 87: 674.
<https://www.ncbi.nlm.nih.gov/pubmed/11350411>
464. Franco, I. Overactive bladder in children. Part 2: Management. *J Urol*, 2007. 178: 769.
<https://www.ncbi.nlm.nih.gov/pubmed/17631323>
465. Goessl, C., *et al.* Urodynamic effects of oral oxybutynin chloride in children with myelomeningocele and detrusor hyperreflexia. *Urology*, 1998. 51: 94.
<https://www.ncbi.nlm.nih.gov/pubmed/9457296>
466. Haferkamp, A., *et al.* Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. *Spinal Cord*, 2000. 38: 250.
<https://www.ncbi.nlm.nih.gov/pubmed/10822396>
467. Mahanta, K., *et al.* Comparative efficacy and safety of extended-release and instant-release tolterodine in children with neural tube defects having cystometric abnormalities. *J Pediatr Urol*, 2008. 4: 118.
<https://www.ncbi.nlm.nih.gov/pubmed/18631906>
468. Austin, P.F., *et al.* Alpha-adrenergic blockade in children with neuropathic and nonneuropathic voiding dysfunction. *J Urol*, 1999. 162: 1064.
<https://www.ncbi.nlm.nih.gov/pubmed/10458432>
469. Deshpande, A.V., *et al.* Study of botulinum toxin A in neurogenic bladder due to spina bifida in children. *ANZ J Surg*, 2010. 80: 250.
<https://www.ncbi.nlm.nih.gov/pubmed/20575951>
470. Game, X., *et al.* Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *J Pediatr Urol*, 2009. 5: 156.
<https://www.ncbi.nlm.nih.gov/pubmed/19264554>
471. Mangera, A., *et al.* Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). *Eur Urol*, 2011. 60: 784.
<https://www.ncbi.nlm.nih.gov/pubmed/21782318>

472. Schulte-Baukloh, H., *et al.* Repeated botulinum-A toxin injections in treatment of children with neurogenic detrusor overactivity. *Urology*, 2005. 66: 865.
<https://www.ncbi.nlm.nih.gov/pubmed/16230156>
473. Schulte-Baukloh, H., *et al.* Botulinum-A toxin in the treatment of neurogenic bladder in children. *Pediatrics*, 2002. 110: 420.
<https://www.ncbi.nlm.nih.gov/pubmed/12814690>
474. Leippold, T., *et al.* Botulinum toxin as a new therapy option for voiding disorders: current state of the art. *Eur Urol*, 2003. 44: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/12875934>
475. Lusuardi, L., *et al.* [Minimally invasive, safe treatment of the neurogenic bladder with botulinum-A-toxin in children with myelomeningocele]. *Aktuelle Urol*, 2004. 35: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/14997415>
476. Schroder, A., *et al.* New strategies for medical management of overactive bladder in children. *Curr Opin Urol*, 2010. 20: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/21475074>
477. Schurch, B., *et al.* Botulinum toxin injections for paediatric incontinence. *Curr Opin Urol*, 2005. 15: 264.
<https://www.ncbi.nlm.nih.gov/pubmed/15928517>
478. Smith, C.P., *et al.* Emerging role of botulinum toxin in the treatment of neurogenic and non-neurogenic voiding dysfunction. *Curr Urol Rep*, 2002. 3: 382.
<https://www.ncbi.nlm.nih.gov/pubmed/12354347>
479. Akbar, M., *et al.* Repeated botulinum-A toxin injections in the treatment of myelodysplastic children and patients with spinal cord injuries with neurogenic bladder dysfunction. *BJU Int*, 2007. 100: 639.
<https://www.ncbi.nlm.nih.gov/pubmed/17532858>
480. DasGupta, R., *et al.* Botulinum toxin in paediatric urology: a systematic literature review. *Pediatr Surg Int*, 2009. 25: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/18953547>
481. Kajbafzadeh, A.M., *et al.* Intravesical injection of botulinum toxin type A: management of neuropathic bladder and bowel dysfunction in children with myelomeningocele. *Urology*, 2006. 68: 1091.
<https://www.ncbi.nlm.nih.gov/pubmed/17113899>
482. Franco, I., *et al.* The use of botulinum toxin A injection for the management of external sphincter dyssynergia in neurologically normal children. *J Urol*, 2007. 178: 1775.
<https://www.ncbi.nlm.nih.gov/pubmed/17707430>
483. Mokhless, I., *et al.* Botulinum A toxin urethral sphincter injection in children with nonneurogenic neurogenic bladder. *J Urol*, 2006. 176: 1767.
<https://www.ncbi.nlm.nih.gov/pubmed/16945643>
484. Younoszai, M.K. Stooling problems in patients with myelomeningocele. *South Med J*, 1992. 85: 718.
<https://www.ncbi.nlm.nih.gov/pubmed/1631686>
485. Aksnes, G., *et al.* Appendicostomy for antegrade enema: effects on somatic and psychosocial functioning in children with myelomeningocele. *Pediatrics*, 2002. 109: 484.
<https://www.ncbi.nlm.nih.gov/pubmed/11875145>
486. Krogh, K., *et al.* [Treatment of anal incontinence and constipation with transanal irrigation]. *Ugeskr Laeger*, 1999. 161: 253.
<https://www.ncbi.nlm.nih.gov/pubmed/10025223>
487. Squire, R., *et al.* The clinical application of the Malone antegrade colonic enema. *J Pediatr Surg*, 1993. 28: 1012.
<https://www.ncbi.nlm.nih.gov/pubmed/8229586>
488. Van Savage, J.G., *et al.* Laparoscopic antegrade continence enema in situ appendix procedure for refractory constipation and overflow fecal incontinence in children with spina bifida. *J Urol*, 2000. 164: 1084.
<https://www.ncbi.nlm.nih.gov/pubmed/10958747>
489. Whitehead, W.E., *et al.* Treatment options for fecal incontinence. *Dis Colon Rectum*, 2001. 44: 131.
<https://www.ncbi.nlm.nih.gov/pubmed/11805574>
490. Loening-Baucke, V., *et al.* Biofeedback training for patients with myelomeningocele and fecal incontinence. *Dev Med Child Neurol*, 1988. 30: 781.
<https://www.ncbi.nlm.nih.gov/pubmed/3234607>

491. Marshall, D.F., *et al.* Altered bladder and bowel function following cutaneous electrical field stimulation in children with spina bifida--interim results of a randomized double-blind placebo-controlled trial. *Eur J Pediatr Surg*, 1997. 7 Suppl 1: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/9497117>
492. Hansson, S., *et al.* Untreated asymptomatic bacteriuria in girls: I--Stability of urinary isolates. *Bmj*, 1989. 298: 853.
<https://www.ncbi.nlm.nih.gov/pubmed/2497822>
493. Hansson, S., *et al.* Untreated bacteriuria in asymptomatic girls with renal scarring. *Pediatrics*, 1989. 84: 964.
<https://www.ncbi.nlm.nih.gov/pubmed/2587151>
494. Hansson, S., *et al.* Untreated asymptomatic bacteriuria in girls: II--Effect of phenoxymethylpenicillin and erythromycin given for intercurrent infections. *Bmj*, 1989. 298: 856.
<https://www.ncbi.nlm.nih.gov/pubmed/2497823>
495. Johnson, H.W., *et al.* A short-term study of nitrofurantoin prophylaxis in children managed with clean intermittent catheterization. *Pediatrics*, 1994. 93: 752.
<https://www.ncbi.nlm.nih.gov/pubmed/8165073>
496. Schlager, T.A., *et al.* Nitrofurantoin prophylaxis for bacteriuria and urinary tract infection in children with neurogenic bladder on intermittent catheterization. *J Pediatr*, 1998. 132: 704.
<https://www.ncbi.nlm.nih.gov/pubmed/9580774>
497. Nguyen, D.H., *et al.* Gastric bladder reconstruction. *Urol Clin North Am*, 1991. 18: 649.
<https://www.ncbi.nlm.nih.gov/pubmed/1949398>
498. Bandi, G., *et al.* Comparison of traditional enterocystoplasty and seromuscular colocolocystoplasty lined with urothelium. *J Pediatr Urol*, 2007. 3: 484.
<https://www.ncbi.nlm.nih.gov/pubmed/18947800>
499. Duel, B.P., *et al.* Alternative techniques for augmentation cystoplasty. *J Urol*, 1998. 159: 998.
<https://www.ncbi.nlm.nih.gov/pubmed/9474216>
500. Austin, P.F., *et al.* Advantages of rectus fascial slings for urinary incontinence in children with neuropathic bladders. *J Urol*, 2001. 165: 2369.
<https://www.ncbi.nlm.nih.gov/pubmed/11398778>
501. Guys, J.M., *et al.* Endoscopic treatment of urinary incontinence: long-term evaluation of the results. *J Urol*, 2001. 165: 2389.
<https://www.ncbi.nlm.nih.gov/pubmed/11371983>
502. Holmes, N.M., *et al.* Placement of artificial urinary sphincter in children and simultaneous gastrocystoplasty. *J Urol*, 2001. 165: 2366.
<https://www.ncbi.nlm.nih.gov/pubmed/11371944>
503. Kassouf, W., *et al.* Collagen injection for treatment of urinary incontinence in children. *J Urol*, 2001. 165: 1666.
<https://www.ncbi.nlm.nih.gov/pubmed/11342951>
504. Kryger, J.V., *et al.* Long-term results of artificial urinary sphincters in children are independent of age at implantation. *J Urol*, 2001. 165: 2377.
<https://www.ncbi.nlm.nih.gov/pubmed/11371981>
505. Naglo, A.S. Continence training of children with neurogenic bladder and detrusor hyperactivity: effect of atropine. *Scand J Urol Nephrol*, 1982. 16: 211.
<https://www.ncbi.nlm.nih.gov/pubmed/7163785>
506. Herndon, C.D., *et al.* The Indiana experience with artificial urinary sphincters in children and young adults. *J Urol*, 2003. 169: 650.
<https://www.ncbi.nlm.nih.gov/pubmed/12544336>
507. Medel, R., *et al.* Urinary continence outcome after augmentation ileocystoplasty as a single surgical procedure in patients with myelodysplasia. *J Urol*, 2002. 168: 1849.
<https://www.ncbi.nlm.nih.gov/pubmed/12352374>
508. Mitchell, M.E., *et al.* Intestinocystoplasty and total bladder replacement in children and young adults: followup in 129 cases. *J Urol*, 1987. 138: 579.
<https://www.ncbi.nlm.nih.gov/pubmed/3625861>
509. Shekarriz, B., *et al.* Surgical complications of bladder augmentation: comparison between various enterocystoplasties in 133 patients. *Urology*, 2000. 55: 123.
<https://www.ncbi.nlm.nih.gov/pubmed/10654908>
510. Balachandra, B., *et al.* Adenocarcinoma arising in a gastrocystoplasty. *J Clin Pathol*, 2007. 60: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/17213351>
511. Castellan, M., *et al.* Tumor in bladder reservoir after gastrocystoplasty. *J Urol*, 2007. 178: 1771.
<https://www.ncbi.nlm.nih.gov/pubmed/17707009>

512. Husmann, D.A., *et al.* Long-term follow up of enteric bladder augmentations: the risk for malignancy. *J Pediatr Urol*, 2008. 4: 381.
<https://www.ncbi.nlm.nih.gov/pubmed/18653384>
513. Soergel, T.M., *et al.* Transitional cell carcinoma of the bladder following augmentation cystoplasty for the neuropathic bladder. *J Urol*, 2004. 172: 1649.
<https://www.ncbi.nlm.nih.gov/pubmed/15371782>
514. Sung, M.T., *et al.* Urothelial carcinoma following augmentation cystoplasty: an aggressive variant with distinct clinicopathological characteristics and molecular genetic alterations. *Histopathology*, 2009. 55: 161.
<https://www.ncbi.nlm.nih.gov/pubmed/19694823>
515. Vemulakonda, V.M., *et al.* Metastatic adenocarcinoma after augmentation gastrocystoplasty. *J Urol*, 2008. 179: 1094.
<https://www.ncbi.nlm.nih.gov/pubmed/18206936>
516. Lebowitz, R.L., *et al.* Neonatal hydronephrosis: 146 cases. *Radiol Clin North Am*, 1977. 15: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/139634>
517. Brown, T., *et al.* Neonatal hydronephrosis in the era of sonography. *AJR Am J Roentgenol*, 1987. 148: 959.
<https://www.ncbi.nlm.nih.gov/pubmed/3034009>
518. Koff, S.A. Problematic ureteropelvic junction obstruction. *J Urol*, 1987. 138: 390.
<https://www.ncbi.nlm.nih.gov/pubmed/3599261>
519. Gunn, T.R., *et al.* Antenatal diagnosis of urinary tract abnormalities by ultrasonography after 28 weeks' gestation: incidence and outcome. *Am J Obstet Gynecol*, 1995. 172: 479.
<https://www.ncbi.nlm.nih.gov/pubmed/7856673>
520. Grignon, A., *et al.* Ureteropelvic junction stenosis: antenatal ultrasonographic diagnosis, postnatal investigation, and follow-up. *Radiology*, 1986. 160: 649.
<https://www.ncbi.nlm.nih.gov/pubmed/3526403>
521. Flashner, S.C., *et al.*, Ureteropelvic junction, in *Clinical Pediatric Urology*. 1976, WB Saunders: Philadelphia.
522. Thomas, D.F. Prenatally detected uropathy: epidemiological considerations. *Br J Urol*, 1998. 81 Suppl 2: 8.
<https://www.ncbi.nlm.nih.gov/pubmed/9602790>
523. Ebel, K.D. Uroradiology in the fetus and newborn: diagnosis and follow-up of congenital obstruction of the urinary tract. *Pediatr Radiol*, 1998. 28: 630.
<https://www.ncbi.nlm.nih.gov/pubmed/9716640>
524. O'Reilly, P., *et al.* Consensus on diuresis renography for investigating the dilated upper urinary tract. Radionuclides in Nephrourology Group. Consensus Committee on Diuresis Renography. *J Nucl Med*, 1996. 37: 1872.
<https://www.ncbi.nlm.nih.gov/pubmed/8917195>
525. Choong, K.K., *et al.* Volume expanded diuretic renography in the postnatal assessment of suspected uretero-pelvic junction obstruction. *J Nucl Med*, 1992. 33: 2094.
<https://www.ncbi.nlm.nih.gov/pubmed/1460498>
526. Reddy, P.P., *et al.* Prenatal diagnosis. Therapeutic implications. *Urol Clin North Am*, 1998. 25: 171.
<https://www.ncbi.nlm.nih.gov/pubmed/9633572>
527. Braga, L.H., *et al.* Pilot randomized, placebo controlled trial to investigate the effect of antibiotic prophylaxis on the rate of urinary tract infection in infants with prenatal hydronephrosis. *J Urol*, 2014. 191: 1501.
<https://www.ncbi.nlm.nih.gov/pubmed/24679865>
528. Craig, J., *et al.*, Long-term antibiotics to prevent urinary tract infection in children with isolated vesicoureteric reflux: a placebo-controlled randomized trial., in *Australian and New Zealand Society of Nephrology 38th Annual Scientific Meeting 2002: Sydney*.
529. Novick, A.C., *et al.*, *Surgery of the kidney*, in *Campbell's Urology*. 1998, WB Saunders: Philadelphia.
530. Fernbach, S.K., *et al.* Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. *Pediatr Radiol*, 1993. 23: 478.
<https://www.ncbi.nlm.nih.gov/pubmed/8255658>
531. Tasian, G.E., *et al.* The robotic-assisted laparoscopic pyeloplasty: gateway to advanced reconstruction. *Urol Clin North Am*, 2015. 42: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/25455175>
532. Reddy, M.N., *et al.* The laparoscopic pyeloplasty: is there a role in the age of robotics? *Urol Clin North Am*, 2015. 42: 43.
<https://www.ncbi.nlm.nih.gov/pubmed/25455171>

533. Huang, Y., *et al.* An updated meta-analysis of laparoscopic versus open pyeloplasty for ureteropelvic junction obstruction in children. *Int J Clin Exp Med*, 2015. 8: 4922.
<https://www.ncbi.nlm.nih.gov/pubmed/26131065>
534. Trevisani, L.F., *et al.* Current controversies in pediatric urologic robotic surgery. *Curr Opin Urol*, 2013. 23: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/23169150>
535. Cundy, T.P., *et al.* Meta-analysis of robot-assisted vs conventional laparoscopic and open pyeloplasty in children. *BJU Int*, 2014. 114: 582.
<https://www.ncbi.nlm.nih.gov/pubmed/25383399>
536. Arena, F., *et al.* Conservative treatment in primary neonatal megaureter. *Eur J Pediatr Surg*, 1998. 8: 347.
<https://www.ncbi.nlm.nih.gov/pubmed/9926303>
537. Peters, C.A., *et al.* Congenital obstructed megaureters in early infancy: diagnosis and treatment. *J Urol*, 1989. 142: 641.
<https://www.ncbi.nlm.nih.gov/pubmed/2746792>
538. Onen, A., *et al.* Long-term followup of prenatally detected severe bilateral newborn hydronephrosis initially managed nonoperatively. *J Urol*, 2002. 168: 1118.
<https://www.ncbi.nlm.nih.gov/pubmed/12187248>
539. Shukla, A.R., *et al.* Prenatally detected primary megaureter: a role for extended followup. *J Urol*, 2005. 173: 1353.
<https://www.ncbi.nlm.nih.gov/pubmed/15758800>
540. Sripathi, V., *et al.* Primary obstructive megaureter. *J Pediatr Surg*, 1991. 26: 826.
<https://www.ncbi.nlm.nih.gov/pubmed/1895193>
541. Fanos, V., *et al.* Antibiotics or surgery for vesicoureteric reflux in children. *Lancet*, 2004. 364: 1720.
<https://www.ncbi.nlm.nih.gov/pubmed/15530633>
542. Sargent, M.A. What is the normal prevalence of vesicoureteral reflux? *Pediatr Radiol*, 2000. 30: 587.
<https://www.ncbi.nlm.nih.gov/pubmed/11009294>
543. Skoog, S.J., *et al.* Pediatric Vesicoureteral Reflux Guidelines Panel Summary Report: Clinical Practice Guidelines for Screening Siblings of Children With Vesicoureteral Reflux and Neonates/ Infants With Prenatal Hydronephrosis. *J Urol*, 2010. 184: 1145.
<https://www.ncbi.nlm.nih.gov/pubmed/20650494>
544. Estrada, C.R., Jr., *et al.* Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. *J Urol*, 2009. 182: 1535.
<https://www.ncbi.nlm.nih.gov/pubmed/19683762>
545. Pirker, M.E., *et al.* Renal scarring in familial vesicoureteral reflux: is prevention possible? *J Urol*, 2006. 176: 1842.
<https://www.ncbi.nlm.nih.gov/pubmed/16945668>
546. Pirker, M.E., *et al.* Familial vesicoureteral reflux: influence of sex on prevalence and expression. *J Urol*, 2006. 176: 1776.
<https://www.ncbi.nlm.nih.gov/pubmed/16945647>
547. Hannula, A., *et al.* Vesicoureteral reflux in children with suspected and proven urinary tract infection. *Pediatr Nephrol*, 2010. 25: 1463.
<https://www.ncbi.nlm.nih.gov/pubmed/20467791>
548. Menezes, M., *et al.* Familial vesicoureteral reflux--is screening beneficial? *J Urol*, 2009. 182: 1673.
<https://www.ncbi.nlm.nih.gov/pubmed/19692047>
549. Alsaywid, B.S., *et al.* High grade primary vesicoureteral reflux in boys: long-term results of a prospective cohort study. *J Urol*, 2010. 184: 1598.
<https://www.ncbi.nlm.nih.gov/pubmed/20728178>
550. Noe, H.N. The long-term results of prospective sibling reflux screening. *J Urol*, 1992. 148: 1739.
<https://www.ncbi.nlm.nih.gov/pubmed/1433599>
551. Ural, Z., *et al.* Bladder dynamics and vesicoureteral reflux: factors associated with idiopathic lower urinary tract dysfunction in children. *J Urol*, 2008. 179: 1564.
<https://www.ncbi.nlm.nih.gov/pubmed/18295262>
552. Sillen, U., *et al.* The Swedish reflux trial in children: v. Bladder dysfunction. *J Urol*, 2010. 184: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/20488469>
553. Sjostrom, S., *et al.* Spontaneous resolution of high grade infantile vesicoureteral reflux. *J Urol*, 2004. 172: 694.
<https://www.ncbi.nlm.nih.gov/pubmed/15247764>

554. Esbjorner, E., *et al.* Management of children with dilating vesico-ureteric reflux in Sweden. *Acta Paediatr*, 2004. 93: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/14989437>
555. Knudson, M.J., *et al.* Predictive factors of early spontaneous resolution in children with primary vesicoureteral reflux. *J Urol*, 2007. 178: 1684.
<https://www.ncbi.nlm.nih.gov/pubmed/17707023>
556. Sjostrom, S., *et al.* Predictive factors for resolution of congenital high grade vesicoureteral reflux in infants: results of univariate and multivariate analyses. *J Urol*, 2010. 183: 1177.
<https://www.ncbi.nlm.nih.gov/pubmed/20096864>
557. Yeung, C.K., *et al.* Renal and bladder functional status at diagnosis as predictive factors for the outcome of primary vesicoureteral reflux in children. *J Urol*, 2006. 176: 1152.
<https://www.ncbi.nlm.nih.gov/pubmed/16890714>
558. Mohanan, N., *et al.* Renal parenchymal damage in intermediate and high grade infantile vesicoureteral reflux. *J Urol*, 2008. 180: 1635.
<https://www.ncbi.nlm.nih.gov/pubmed/18708232>
559. Olbing, H., *et al.* New renal scars in children with severe VUR: a 10-year study of randomized treatment. *Pediatr Nephrol*, 2003. 18: 1128.
<https://www.ncbi.nlm.nih.gov/pubmed/14523634>
560. Peters, C., *et al.* Vesicoureteral reflux associated renal damage: congenital reflux nephropathy and acquired renal scarring. *J Urol*, 2010. 184: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/20483150>
561. Coplen, D.E., *et al.* Correlation of prenatal and postnatal ultrasound findings with the incidence of vesicoureteral reflux in children with fetal renal pelvic dilatation. *J Urol*, 2008. 180: 1631.
<https://www.ncbi.nlm.nih.gov/pubmed/18718617>
562. Estrada, C.R., *et al.* Vesicoureteral reflux and urinary tract infection in children with a history of prenatal hydronephrosis--should voiding cystourethrography be performed in cases of postnatally persistent grade II hydronephrosis? *J Urol*, 2009. 181: 801.
<https://www.ncbi.nlm.nih.gov/pubmed/19095265>
563. Lee, R.S., *et al.* Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. *Pediatrics*, 2006. 118: 586.
<https://www.ncbi.nlm.nih.gov/pubmed/16882811>
564. Mallik, M., *et al.* Antenatally detected urinary tract abnormalities: more detection but less action. *Pediatr Nephrol*, 2008. 23: 897.
<https://www.ncbi.nlm.nih.gov/pubmed/18278521>
565. Phan, V., *et al.* Vesicoureteral reflux in infants with isolated antenatal hydronephrosis. *Pediatr Nephrol*, 2003. 18: 1224.
<https://www.ncbi.nlm.nih.gov/pubmed/14586679>
566. Ylinen, E., *et al.* Risk of renal scarring in vesicoureteral reflux detected either antenatally or during the neonatal period. *Urology*, 2003. 61: 1238.
<https://www.ncbi.nlm.nih.gov/pubmed/12809909>
567. Leonardo, C.R., *et al.* Risk factors for renal scarring in children and adolescents with lower urinary tract dysfunction. *Pediatr Nephrol*, 2007. 22: 1891.
<https://www.ncbi.nlm.nih.gov/pubmed/17874252>
568. Naseer, S.R., *et al.* New renal scars in children with urinary tract infections, vesicoureteral reflux and voiding dysfunction: a prospective evaluation. *J Urol*, 1997. 158: 566.
<https://www.ncbi.nlm.nih.gov/pubmed/9224361>
569. Blumenthal, I. Vesicoureteric reflux and urinary tract infection in children. *Postgrad Med J*, 2006. 82: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/16397077>
570. Darge, K., *et al.* Current status of vesicoureteral reflux diagnosis. *World J Urol*, 2004. 22: 88.
<https://www.ncbi.nlm.nih.gov/pubmed/15173954>
571. Lebowitz, R.L., *et al.* International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. *Pediatr Radiol*, 1985. 15: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/3975102>
572. Westwood, M.E., *et al.* Further investigation of confirmed urinary tract infection (UTI) in children under five years: a systematic review. *BMC Pediatr*, 2005. 5: 2.
<https://www.ncbi.nlm.nih.gov/pubmed/15769296>
573. Snow, B.W., *et al.* Non-invasive vesicoureteral reflux imaging. *J Pediatr Urol*, 2010. 6: 543.
<https://www.ncbi.nlm.nih.gov/pubmed/20488755>

574. Darge, K. Voiding urosonography with US contrast agents for the diagnosis of vesicoureteric reflux in children. II. Comparison with radiological examinations. *Pediatr Radiol*, 2008. 38: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/17639371>
575. Papadopoulou, F., *et al.* Harmonic voiding urosonography with a second-generation contrast agent for the diagnosis of vesicoureteral reflux. *Pediatr Radiol*, 2009. 39: 239.
<https://www.ncbi.nlm.nih.gov/pubmed/19096835>
576. Takazakura, R., *et al.* Magnetic resonance voiding cystourethrography for vesicoureteral reflux. *J Magn Reson Imaging*, 2007. 25: 170.
<https://www.ncbi.nlm.nih.gov/pubmed/17154372>
577. Medical versus surgical treatment of primary vesicoureteral reflux: report of the International Reflux Study Committee. *Pediatrics*, 1981. 67: 392.
<https://www.ncbi.nlm.nih.gov/pubmed/7017578>
578. Scherz, H.C., *et al.* The selective use of dimercaptosuccinic acid renal scans in children with vesicoureteral reflux. *J Urol*, 1994. 152: 628.
<https://www.ncbi.nlm.nih.gov/pubmed/8021985>
579. Hoberman, A., *et al.* Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med*, 2003. 348: 195.
<https://www.ncbi.nlm.nih.gov/pubmed/12529459>
580. Grazioli, S., *et al.* Antenatal and postnatal ultrasound in the evaluation of the risk of vesicoureteral reflux. *Pediatr Nephrol*, 2010. 25: 1687.
<https://www.ncbi.nlm.nih.gov/pubmed/20524012>
581. Lidefelt, K.J., *et al.* Antenatal hydronephrosis: infants with minor postnatal dilatation do not need prophylaxis. *Pediatr Nephrol*, 2008. 23: 2021.
<https://www.ncbi.nlm.nih.gov/pubmed/18560902>
582. Hafez, A.T., *et al.* Analysis of trends on serial ultrasound for high grade neonatal hydronephrosis. *J Urol*, 2002. 168: 1518.
<https://www.ncbi.nlm.nih.gov/pubmed/12352447>
583. Lee, J.H., *et al.* Nonrefluxing neonatal hydronephrosis and the risk of urinary tract infection. *J Urol*, 2008. 179: 1524.
<https://www.ncbi.nlm.nih.gov/pubmed/18295269>
584. Sidhu, G., *et al.* Outcome of isolated antenatal hydronephrosis: a systematic review and meta-analysis. *Pediatr Nephrol*, 2006. 21: 218.
<https://www.ncbi.nlm.nih.gov/pubmed/16362721>
585. Houle, A.M., *et al.* Impact of early screening for reflux in siblings on the detection of renal damage. *BJU Int*, 2004. 94: 123.
<https://www.ncbi.nlm.nih.gov/pubmed/15217445>
586. Puri, P., *et al.* Urinary tract infection and renal damage in sibling vesicoureteral reflux. *J Urol*, 1998. 160: 1028.
<https://www.ncbi.nlm.nih.gov/pubmed/9719271>
587. Shaikh, N., *et al.* Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. *JAMA Pediatr*, 2014. 168: 893.
<https://www.ncbi.nlm.nih.gov/pubmed/25089634>
588. Hansson, S., *et al.* Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. *J Urol*, 2004. 172: 1071.
<https://www.ncbi.nlm.nih.gov/pubmed/15311040>
589. Herz, D., *et al.* 5-year prospective results of dimercapto-succinic acid imaging in children with febrile urinary tract infection: proof that the top-down approach works. *J Urol*, 2010. 184: 1703.
<https://www.ncbi.nlm.nih.gov/pubmed/20728131>
590. Preda, I., *et al.* Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. *J Pediatr*, 2007. 151: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/18035134>
591. Colen, J., *et al.* Dysfunctional elimination syndrome is a negative predictor for vesicoureteral reflux. *J Pediatr Urol*, 2006. 2: 312.
<https://www.ncbi.nlm.nih.gov/pubmed/18947628>
592. Elder, J.S., *et al.* Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J Urol*, 1997. 157: 1846.
<https://www.ncbi.nlm.nih.gov/pubmed/9112544>
593. Dias, C.S., *et al.* Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. *Pediatr Infect Dis J*, 2010. 29: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/20135833>

594. Wheeler, D.M., *et al.* Interventions for primary vesicoureteric reflux. *Cochrane Database Syst Rev*, 2004: CD001532.
<https://www.ncbi.nlm.nih.gov/pubmed/15266449>
595. Williams, G.J., *et al.* Long-term antibiotics for preventing recurrent urinary tract infection in children. *Cochrane Database Syst Rev*, 2006: CD001534.
<https://www.ncbi.nlm.nih.gov/pubmed/16855971>
596. Singh-Grewal, D., *et al.* Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies. *Arch Dis Child*, 2005. 90: 853.
<https://www.ncbi.nlm.nih.gov/pubmed/15890696>
597. Brandstrom, P., *et al.* The Swedish reflux trial in children: IV. Renal damage. *J Urol*, 2010. 184: 292.
<https://www.ncbi.nlm.nih.gov/pubmed/20494369>
598. Greenfield, S.P. Antibiotic prophylaxis in pediatric urology: an update. *Curr Urol Rep*, 2011. 12: 126.
<https://www.ncbi.nlm.nih.gov/pubmed/21229337>
599. Greenfield, S.P., *et al.* Vesicoureteral reflux: the RIVUR study and the way forward. *J Urol*, 2008. 179: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/18076937>
600. Brandstrom, P., *et al.* The Swedish reflux trial in children: III. Urinary tract infection pattern. *J Urol*, 2010. 184: 286.
<https://www.ncbi.nlm.nih.gov/pubmed/20488494>
601. Hoberman, A., *et al.* Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*, 2014. 370: 2367.
<https://www.ncbi.nlm.nih.gov/pubmed/24795142>
602. Mathews, R., *et al.* The role of antimicrobial prophylaxis in the management of children with vesicoureteral reflux--the RIVUR study outcomes. *Adv Chronic Kidney Dis*, 2015. 22: 325.
<https://www.ncbi.nlm.nih.gov/pubmed/26088078>
603. Hidas, G., *et al.* Predicting the Risk of Breakthrough Urinary Tract Infections: Primary Vesicoureteral Reflux. *J Urol*, 2015. 194: 1396.
<https://www.ncbi.nlm.nih.gov/pubmed/26066405>
604. de Bessa, J., Jr., *et al.* Antibiotic prophylaxis for prevention of febrile urinary tract infections in children with vesicoureteral reflux: a meta-analysis of randomized, controlled trials comparing dilated to nondilated vesicoureteral reflux. *J Urol*, 2015. 193: 1772.
<https://www.ncbi.nlm.nih.gov/pubmed/25817142>
605. Dogan, H.S., *et al.* Factors affecting the success of endoscopic treatment of vesicoureteral reflux and comparison of two dextranomer based bulking agents: does bulking substance matter? *J Pediatr Urol*, 2015. 11: 90.e1.
<https://www.ncbi.nlm.nih.gov/pubmed/24095906>
606. Kocherov, S., *et al.* Multicenter survey of endoscopic treatment of vesicoureteral reflux using polyacrylate-polyalcohol bulking copolymer (Vantris). *Urology*, 2014. 84: 689.
<https://www.ncbi.nlm.nih.gov/pubmed/25168553>
607. Puri, P., *et al.* Multicenter survey of endoscopic treatment of vesicoureteral reflux using polytetrafluoroethylene. *J Urol*, 1998. 160: 1007.
<https://www.ncbi.nlm.nih.gov/pubmed/9719265>
608. Steyaert, H., *et al.* Migration of PTFE paste particles to the kidney after treatment for vesico-ureteric reflux. *BJU Int*, 2000. 85: 168.
<https://www.ncbi.nlm.nih.gov/pubmed/10619969>
609. Lightner, D.J. Review of the available urethral bulking agents. *Curr Opin Urol*, 2002. 12: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/12072655>
610. Elder, J.S., *et al.* Endoscopic therapy for vesicoureteral reflux: a meta-analysis. I. Reflux resolution and urinary tract infection. *J Urol*, 2006. 175: 716.
<https://www.ncbi.nlm.nih.gov/pubmed/16407037>
611. Holmdahl, G., *et al.* The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. *J Urol*, 2010. 184: 280.
<https://www.ncbi.nlm.nih.gov/pubmed/20488469>
612. Duckett, J.W., *et al.* Surgical results: International Reflux Study in Children--United States branch. *J Urol*, 1992. 148: 1674.
<https://www.ncbi.nlm.nih.gov/pubmed/9507881>
613. Lipski, B.A., *et al.* Voiding dysfunction after bilateral extravesical ureteral reimplantation. *J Urol*, 1998. 159: 1019.
<https://www.ncbi.nlm.nih.gov/pubmed/9474222>

614. Marchini, G.S., *et al.* Robotic assisted laparoscopic ureteral reimplantation in children: case matched comparative study with open surgical approach. *J Urol*, 2011. 185: 1870.
<https://www.ncbi.nlm.nih.gov/pubmed/9474222>
615. Kasturi, S., *et al.* Prospective long-term analysis of nerve-sparing extravesical robotic-assisted laparoscopic ureteral reimplantation. *Urology*, 2012. 79: 680.
<https://www.ncbi.nlm.nih.gov/pubmed/22197530>
616. Austin, J.C., *et al.* Vesicoureteral reflux: who benefits from correction. *Urol Clin North Am*, 2010. 37: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/20569802>
617. Canon, S.J., *et al.* Vesicoscopic cross-trigonal ureteral reimplantation: a minimally invasive option for repair of vesicoureteral reflux. *J Urol*, 2007. 178: 269.
<https://www.ncbi.nlm.nih.gov/pubmed/17499791>
618. Chung, P.H., *et al.* Comparing open and pneumovesical approach for ureteric reimplantation in pediatric patients--a preliminary review. *J Pediatr Surg*, 2008. 43: 2246.
<https://www.ncbi.nlm.nih.gov/pubmed/19040945>
619. El-Ghoneimi, A. Paediatric laparoscopic surgery. *Curr Opin Urol*, 2003. 13: 329.
<https://www.ncbi.nlm.nih.gov/pubmed/12811298>
620. Janetschek, G., *et al.* Laparoscopic ureteral anti-reflux plasty reimplantation. First clinical experience. *Ann Urol (Paris)*, 1995. 29: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/7645993>
621. Jayanthi, V., *et al.* Vesicoscopic ureteral reimplantation: a minimally invasive technique for the definitive repair of vesicoureteral reflux. *Adv Urol*, 2008: 973616.
<https://www.ncbi.nlm.nih.gov/pubmed/17499791>
622. Riquelme, M., *et al.* Laparoscopic extravesical transperitoneal approach for vesicoureteral reflux. *J Laparoendosc Adv Surg Tech A*, 2006. 16: 312.
<https://www.ncbi.nlm.nih.gov/pubmed/16796449>
623. Grimsby, G.M., *et al.* Multi-institutional review of outcomes of robot-assisted laparoscopic extravesical ureteral reimplantation. *J Urol*, 2015. 193: 1791.
<https://www.ncbi.nlm.nih.gov/pubmed/25301094>
624. Straub, M., *et al.* Diagnosis and metaphylaxis of stone disease. Consensus concept of the National Working Committee on Stone Disease for the upcoming German Urolithiasis Guideline. *World J Urol*, 2005. 23: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/16315051>
625. Metcalfe, P.D., *et al.* What is the need for additional bladder surgery after bladder augmentation in childhood? *J Urol*, 2006. 176: 1801.
<https://www.ncbi.nlm.nih.gov/pubmed/16945653>
626. Bush, N.C., *et al.* Hospitalizations for pediatric stone disease in United States, 2002-2007. *J Urol*, 2010. 183: 1151.
<https://www.ncbi.nlm.nih.gov/pubmed/20096871>
627. Novak, T.E., *et al.* Sex prevalence of pediatric kidney stone disease in the United States: an epidemiologic investigation. *Urology*, 2009. 74: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/19428065>
628. Tasian, G.E., *et al.* Annual Incidence of Nephrolithiasis among Children and Adults in South Carolina from 1997 to 2012. *Clin J Am Soc Nephrol*, 2016. 11: 488.
<https://www.ncbi.nlm.nih.gov/pubmed/26769765>
629. Sas, D.J., *et al.* Increasing incidence of kidney stones in children evaluated in the emergency department. *J Pediatr*, 2010. 157: 132.
<https://www.ncbi.nlm.nih.gov/pubmed/20362300>
630. Kirejczyk, J.K., *et al.* An association between kidney stone composition and urinary metabolic disturbances in children. *J Pediatr Urol*, 2014. 10: 130.
<https://www.ncbi.nlm.nih.gov/pubmed/23953243>
631. Kruse, K., *et al.* Reference values for urinary calcium excretion and screening for hypercalciuria in children and adolescents. *Eur J Pediatr*, 1984. 143: 25.
<https://www.ncbi.nlm.nih.gov/pubmed/6510426>
632. Sargent, J.D., *et al.* Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr*, 1993. 123: 393.
<https://www.ncbi.nlm.nih.gov/pubmed/8355114>
633. Stapleton, F.B., *et al.* Urinary excretion of calcium following an oral calcium loading test in healthy children. *Pediatrics*, 1982. 69: 594.
<https://www.ncbi.nlm.nih.gov/pubmed/7079015>

634. Stapleton, F.B., *et al.* Hypercalciuria in children with urolithiasis. *Am J Dis Child*, 1982. 136: 675.
<https://www.ncbi.nlm.nih.gov/pubmed/7102617>
635. Borghi, L., *et al.* Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med*, 2002. 346: 77.
<https://www.ncbi.nlm.nih.gov/pubmed/>
636. Curhan, G.C., *et al.* A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med*, 1993. 328: 833.
<https://www.ncbi.nlm.nih.gov/pubmed/8441427>
637. Bartosh, S.M. Medical management of pediatric stone disease. *Urol Clin North Am*, 2004. 31: 575.
<https://www.ncbi.nlm.nih.gov/pubmed/15313066>
638. Preminger, G.M., *et al.* Eventual attenuation of hypocalciuric response to hydrochlorothiazide in absorptive hypercalciuria. *J Urol*, 1987. 137: 1104.
<https://www.ncbi.nlm.nih.gov/pubmed/3586136>
639. Choi, J.N., *et al.* Low-dose thiazide diuretics in children with idiopathic renal hypercalciuria. *Acta Paediatr*, 2011. 100: e71.
<https://www.ncbi.nlm.nih.gov/pubmed/21284722>
640. Naseri, M., *et al.* Role of high-dose hydrochlorothiazide in idiopathic hypercalciuric urolithiasis of childhood. *Iran J Kidney Dis*, 2011. 5: 162.
<https://www.ncbi.nlm.nih.gov/pubmed/21525575>
641. Tekin, A., *et al.* Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. *J Urol*, 2002. 168: 2572.
<https://www.ncbi.nlm.nih.gov/pubmed/12441986>
642. Neuhaus, T.J., *et al.* Urinary oxalate excretion in urolithiasis and nephrocalcinosis. *Arch Dis Child*, 2000. 82: 322.
<https://www.ncbi.nlm.nih.gov/pubmed/10735843>
643. Hoppe, B., *et al.* Urinary calcium oxalate saturation in healthy infants and children. *J Urol*, 1997. 158: 557.
<https://www.ncbi.nlm.nih.gov/pubmed/9224359>
644. Turudic, D., *et al.* Calcium oxalate urolithiasis in children: urinary promoters/inhibitors and role of their ratios. *Eur J Pediatr*, 2016. 175: 1959.
<https://www.ncbi.nlm.nih.gov/pubmed/27730307>
645. Morgenstern, B.Z., *et al.* Urinary oxalate and glycolate excretion patterns in the first year of life: a longitudinal study. *J Pediatr*, 1993. 123: 248.
<https://www.ncbi.nlm.nih.gov/pubmed/8345420>
646. Defoor, W., *et al.* Results of a prospective trial to compare normal urine supersaturation in children and adults. *J Urol*, 2005. 174: 1708.
<https://www.ncbi.nlm.nih.gov/pubmed/16148687>
647. Tekin, A., *et al.* A study of the etiology of idiopathic calcium urolithiasis in children: hypocitruria is the most important risk factor. *J Urol*, 2000. 164: 162.
<https://www.ncbi.nlm.nih.gov/pubmed/10840454>
648. Kovacevic, L., *et al.* From hypercalciuria to hypocitruria--a shifting trend in pediatric urolithiasis? *J Urol*, 2012. 188: 1623.
<https://www.ncbi.nlm.nih.gov/pubmed/22910255>
649. Celiksoy, M.H., *et al.* Metabolic disorders in Turkish children with urolithiasis. *Urology*, 2015. 85: 909.
<https://www.ncbi.nlm.nih.gov/pubmed/25817115>
650. Tekin, A., *et al.* Cystine calculi in children: the results of a metabolic evaluation and response to medical therapy. *J Urol*, 2001. 165: 2328.
<https://www.ncbi.nlm.nih.gov/pubmed/11371943>
651. Gabrielsen, J.S., *et al.* Pediatric urinary stone composition in the United States. *J Urol*, 2012. 187: 2182.
<https://www.ncbi.nlm.nih.gov/pubmed/22503021>
652. Rellum, D.M., *et al.* Pediatric urolithiasis in a non-endemic country: a single center experience from The Netherlands. *J Pediatr Urol*, 2014. 10: 155.
<https://www.ncbi.nlm.nih.gov/pubmed/23981680>
653. Bove, P., *et al.* Reexamining the value of hematuria testing in patients with acute flank pain. *J Urol*, 1999. 162: 685.
<https://www.ncbi.nlm.nih.gov/pubmed/10458342>
654. Sternberg, K., *et al.* Pediatric stone disease: an evolving experience. *J Urol*, 2005. 174: 1711.
<https://www.ncbi.nlm.nih.gov/pubmed/16148688>

655. Oner, S., *et al.* Comparison of spiral CT and US in the evaluation of pediatric urolithiasis. *Jbr-btr*, 2004. 87: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/15587558>
656. Memarsadeghi, M., *et al.* Unenhanced multi-detector row CT in patients suspected of having urinary stone disease: effect of section width on diagnosis. *Radiology*, 2005. 235: 530.
<https://www.ncbi.nlm.nih.gov/pubmed/15758192>
657. Strouse, P.J., *et al.* Non-contrast thin-section helical CT of urinary tract calculi in children. *Pediatr Radiol*, 2002. 32: 326.
<https://www.ncbi.nlm.nih.gov/pubmed/11956719>
658. Kwon, J.K., *et al.* Usefulness of low-dose nonenhanced computed tomography with iterative reconstruction for evaluation of urolithiasis: diagnostic performance and agreement between the urologist and the radiologist. *Urology*, 2015. 85: 531.
<https://www.ncbi.nlm.nih.gov/pubmed/25733262>
659. Skolarikos, A., *et al.* Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. *Eur Urol*, 2015. 67: 750.
<https://www.ncbi.nlm.nih.gov/pubmed/25454613>
660. Tekin, A., *et al.* Ureteropelvic junction obstruction and coexisting renal calculi in children: role of metabolic abnormalities. *Urology*, 2001. 57: 542.
<https://www.ncbi.nlm.nih.gov/pubmed/11248635>
661. Alpay, H., *et al.* Clinical and metabolic features of urolithiasis and microlithiasis in children. *Pediatr Nephrol*, 2009. 24: 2203.
<https://www.ncbi.nlm.nih.gov/pubmed/19603196>
662. Raza, A., *et al.* Pediatric urolithiasis: 15 years of local experience with minimally invasive endourological management of pediatric calculi. *J Urol*, 2005. 174: 682.
<https://www.ncbi.nlm.nih.gov/pubmed/16006948>
663. Rizvi, S.A., *et al.* Pediatric urolithiasis: developing nation perspectives. *J Urol*, 2002. 168: 1522.
<https://www.ncbi.nlm.nih.gov/pubmed/12352448>
664. Shahat, A., *et al.* Is Tamsulosin Effective after Shock Wave Lithotripsy for Pediatric Renal Stones? A Randomized, Controlled Study. *J Urol*, 2016. 195: 1284.
<https://www.ncbi.nlm.nih.gov/pubmed/26926538>
665. Velazquez, N., *et al.* Medical expulsive therapy for pediatric urolithiasis: Systematic review and meta-analysis. *J Pediatr Urol*, 2015. 11: 321.
<https://www.ncbi.nlm.nih.gov/pubmed/26165192>
666. Dincel, N., *et al.* Are small residual stone fragments really insignificant in children? *J Pediatr Surg*, 2013. 48: 840.
<https://www.ncbi.nlm.nih.gov/pubmed/23583144>
667. El-Assmy, A., *et al.* Clinically Insignificant Residual Fragments: Is It an Appropriate Term in Children? *Urology*, 2015. 86: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/26126693>
668. Reisiger, K., *et al.* Pediatric nephrolithiasis: does treatment affect renal growth? *Urology*, 2007. 69: 1190.
<https://www.ncbi.nlm.nih.gov/pubmed/17572213>
669. Akin, Y., *et al.* Long-term effects of pediatric extracorporeal shockwave lithotripsy on renal function. *Res Rep Urol*, 2014. 6: 21.
<https://www.ncbi.nlm.nih.gov/pubmed/24892029>
670. Willis, L.R., *et al.* Relationship between kidney size, renal injury, and renal impairment induced by shock wave lithotripsy. *J Am Soc Nephrol*, 1999. 10: 1753.
<https://www.ncbi.nlm.nih.gov/pubmed/10446943>
671. Villanyi, K.K., *et al.* Short-term changes in renal function after extracorporeal shock wave lithotripsy in children. *J Urol*, 2001. 166: 222.
<https://www.ncbi.nlm.nih.gov/pubmed/11435873>
672. Aldridge, R.D., *et al.* Anesthesia for pediatric lithotripsy. *Paediatr Anaesth*, 2006. 16: 236.
<https://www.ncbi.nlm.nih.gov/pubmed/16490086>
673. McLorie, G.A., *et al.* Safety and efficacy of extracorporeal shock wave lithotripsy in infants. *Can J Urol*, 2003. 10: 2051.
<https://www.ncbi.nlm.nih.gov/pubmed/14704109>
674. Aksoy, Y., *et al.* Extracorporeal shock wave lithotripsy in children: experience using a mpl-9000 lithotripter. *World J Urol*, 2004. 22: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/14740160>

675. Vljakovic, M., *et al.* Long-term functional outcome of kidneys in children with urolithiasis after ESWL treatment. *Eur J Pediatr Surg*, 2002. 12: 118.
<https://www.ncbi.nlm.nih.gov/pubmed/12015657>
676. Muslumanoglu, A.Y., *et al.* Extracorporeal shock wave lithotripsy as first line treatment alternative for urinary tract stones in children: a large scale retrospective analysis. *J Urol*, 2003. 170: 2405.
<https://www.ncbi.nlm.nih.gov/pubmed/14634438>
677. Ather, M.H., *et al.* Does size and site matter for renal stones up to 30-mm in size in children treated by extracorporeal lithotripsy? *Urology*, 2003. 61: 212.
<https://www.ncbi.nlm.nih.gov/pubmed/12559298>
678. Ugur, G., *et al.* Anaesthetic/analgesic management of extracorporeal shock wave lithotripsy in paediatric patients. *Paediatr Anaesth*, 2003. 13: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/12535048>
679. Rodrigues Netto, N., Jr., *et al.* Extracorporeal shock wave lithotripsy in children. *J Urol*, 2002. 167: 2164.
<https://www.ncbi.nlm.nih.gov/pubmed/11956471>
680. Afshar, K., *et al.* Outcome of small residual stone fragments following shock wave lithotripsy in children. *J Urol*, 2004. 172: 1600.
<https://www.ncbi.nlm.nih.gov/pubmed/15371769>
681. Tan, A.H., *et al.* Results of shockwave lithotripsy for pediatric urolithiasis. *J Endourol*, 2004. 18: 527.
<https://www.ncbi.nlm.nih.gov/pubmed/15333214>
682. Lottmann, H.B., *et al.* Monotherapy extracorporeal shock wave lithotripsy for the treatment of staghorn calculi in children. *J Urol*, 2001. 165: 2324.
<https://www.ncbi.nlm.nih.gov/pubmed/11371942>
683. Al-Busaidy, S.S., *et al.* Pediatric staghorn calculi: the role of extracorporeal shock wave lithotripsy monotherapy with special reference to ureteral stenting. *J Urol*, 2003. 169: 629.
<https://www.ncbi.nlm.nih.gov/pubmed/12544330>
684. Ozgur Tan, M., *et al.* Extracorporeal shock-wave lithotripsy for treatment of ureteral calculi in paediatric patients. *Pediatr Surg Int*, 2003. 19: 471.
<https://www.ncbi.nlm.nih.gov/pubmed/12736749>
685. Onal, B., *et al.* The impact of caliceal pelvic anatomy on stone clearance after shock wave lithotripsy for pediatric lower pole stones. *J Urol*, 2004. 172: 1082.
<https://www.ncbi.nlm.nih.gov/pubmed/15311043>
686. Ozgur Tan, M., *et al.* The impact of radiological anatomy in clearance of lower calyceal stones after shock wave lithotripsy in paediatric patients. *Eur Urol*, 2003. 43: 188.
<https://www.ncbi.nlm.nih.gov/pubmed/12565778>
687. Demirkesen, O., *et al.* Efficacy of extracorporeal shock wave lithotripsy for isolated lower caliceal stones in children compared with stones in other renal locations. *Urology*, 2006. 67: 170.
<https://www.ncbi.nlm.nih.gov/pubmed/16413356>
688. Hochreiter, W.W., *et al.* Extracorporeal shock wave lithotripsy for distal ureteral calculi: what a powerful machine can achieve. *J Urol*, 2003. 169: 878.
<https://www.ncbi.nlm.nih.gov/pubmed/12576804>
689. Landau, E.H., *et al.* Extracorporeal shock wave lithotripsy is highly effective for ureteral calculi in children. *J Urol*, 2001. 165: 2316.
<https://www.ncbi.nlm.nih.gov/pubmed/11371970>
690. McAdams, S., *et al.* Preoperative Stone Attenuation Value Predicts Success After Shock Wave Lithotripsy in Children. *J Urol*, 2010. 184: 1804.
<http://www.sciencedirect.com/science/article/pii/S0022534710032106>
691. Onal, B., *et al.* Nomogram and scoring system for predicting stone-free status after extracorporeal shock wave lithotripsy in children with urolithiasis. *BJU Int*, 2013. 111: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/22672514>
692. Dogan, H.S., *et al.* A new nomogram for prediction of outcome of pediatric shock-wave lithotripsy. *J Pediatr Urol*, 2015. 11: 84 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/25812469>
693. Wu, H.Y., *et al.* Surgical management of children with urolithiasis. *Urol Clin North Am*, 2004. 31: 589.
<https://www.ncbi.nlm.nih.gov/pubmed/15313067>
694. Desai, M.R., *et al.* Percutaneous nephrolithotomy for complex pediatric renal calculus disease. *J Endourol*, 2004. 18: 23.
<https://www.ncbi.nlm.nih.gov/pubmed/15006048>

695. Soygur, T., *et al.* Hydrodilation of the ureteral orifice in children renders ureteroscopic access possible without any further active dilation. *J Urol*, 2006. 176: 285.
<https://www.ncbi.nlm.nih.gov/pubmed/16753421>
696. Caione, P., *et al.* Endoscopic manipulation of ureteral calculi in children by rigid operative ureterorenoscopy. *J Urol*, 1990. 144: 484.
<https://www.ncbi.nlm.nih.gov/pubmed/2374225>
697. Thomas, J.C., *et al.* Pediatric ureteroscopic stone management. *J Urol*, 2005. 174: 1072.
<https://www.ncbi.nlm.nih.gov/pubmed/18804225>
698. Dogan, H.S., *et al.* Use of the holmium:YAG laser for ureterolithotripsy in children. *BJU Int*, 2004. 94: 131.
<https://www.ncbi.nlm.nih.gov/pubmed/15217447>
699. De Dominicis, M., *et al.* Retrograde ureteroscopy for distal ureteric stone removal in children. *BJU Int*, 2005. 95: 1049.
<https://www.ncbi.nlm.nih.gov/pubmed/15839930>
700. Satar, N., *et al.* Rigid ureteroscopy for the treatment of ureteral calculi in children. *J Urol*, 2004. 172: 298.
<https://www.ncbi.nlm.nih.gov/pubmed/15201799>
701. Raza, A., *et al.* Ureteroscopy in the management of pediatric urinary tract calculi. *J Endourol*, 2005. 19: 151.
<https://www.ncbi.nlm.nih.gov/pubmed/15798409>
702. Bassiri, A., *et al.* Transureteral lithotripsy in pediatric practice. *J Endourol*, 2002. 16: 257.
<https://www.ncbi.nlm.nih.gov/pubmed/12042111>
703. Van Savage, J.G., *et al.* Treatment of distal ureteral stones in children: similarities to the american urological association guidelines in adults. *J Urol*, 2000. 164: 1089.
<https://www.ncbi.nlm.nih.gov/pubmed/10958749>
704. Jackman, S.V., *et al.* Percutaneous nephrolithotomy in infants and preschool age children: experience with a new technique. *Urology*, 1998. 52: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/9763096>
705. ElSheemy, M.S., *et al.* Lower calyceal and renal pelvic stones in preschool children: A comparative study of mini-percutaneous nephrolithotomy versus extracorporeal shockwave lithotripsy. *Int J Urol*, 2016. 23: 564.
<https://www.ncbi.nlm.nih.gov/pubmed/27173126>
706. Badawy, H., *et al.* Percutaneous management of renal calculi: experience with percutaneous nephrolithotomy in 60 children. *J Urol*, 1999. 162: 1710.
<https://www.ncbi.nlm.nih.gov/pubmed/10524919>
707. Dawaba, M.S., *et al.* Percutaneous nephrolithotomy in children: early and late anatomical and functional results. *J Urol*, 2004. 172: 1078.
<https://www.ncbi.nlm.nih.gov/pubmed/15311042>
708. Boormans, J.L., *et al.* Percutaneous nephrolithotomy for treating renal calculi in children. *BJU Int*, 2005. 95: 631.
<https://www.ncbi.nlm.nih.gov/pubmed/15705093>
709. Shokeir, A.A., *et al.* Percutaneous nephrolithotomy in treatment of large stones within horseshoe kidneys. *Urology*, 2004. 64: 426.
<https://www.ncbi.nlm.nih.gov/pubmed/15311042>
710. Sahin, A., *et al.* Percutaneous nephrolithotomy in older children. *J Pediatr Surg*, 2000. 35: 1336.
<https://www.ncbi.nlm.nih.gov/pubmed/10999692>
711. Ozden, E., *et al.* Modified Clavien classification in percutaneous nephrolithotomy: assessment of complications in children. *J Urol*, 2011. 185: 264.
<https://www.ncbi.nlm.nih.gov/pubmed/21074805>
712. Guven, S., *et al.* Successful percutaneous nephrolithotomy in children: multicenter study on current status of its use, efficacy and complications using Clavien classification. *J Urol*, 2011. 185: 1419.
<https://www.ncbi.nlm.nih.gov/pubmed/21334653>
713. Dogan, H.S., *et al.* Percutaneous nephrolithotomy in children: does age matter? *World J Urol*, 2011. 29: 725.
<https://www.ncbi.nlm.nih.gov/pubmed/21590468>
714. Khairy Salem, H., *et al.* Tubeless percutaneous nephrolithotomy in children. *J Pediatr Urol*, 2007. 3: 235.
<https://www.ncbi.nlm.nih.gov/pubmed/18947742>

715. Unsal, A., *et al.* Safety and efficacy of percutaneous nephrolithotomy in infants, preschool age, and older children with different sizes of instruments. *Urology*, 2010. 76: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/20022089>
716. Nouralizadeh, A., *et al.* Experience of percutaneous nephrolithotomy using adult-size instruments in children less than 5 years old. *J Pediatr Urol*, 2009. 5: 351.
<https://www.ncbi.nlm.nih.gov/pubmed/19230776>
717. Ozden, E., *et al.* Percutaneous renal surgery in children with complex stones. *J Pediatr Urol*, 2008. 4: 295.
<https://www.ncbi.nlm.nih.gov/pubmed/18644533>
718. Onal, B., *et al.* Factors affecting complication rates of percutaneous nephrolithotomy in children: results of a multi-institutional retrospective analysis by the Turkish pediatric urology society. *J Urol*, 2014. 191: 777.
<https://www.ncbi.nlm.nih.gov/pubmed/24095906>
719. Bilen, C.Y., *et al.* Tubeless mini percutaneous nephrolithotomy in infants and preschool children: a preliminary report. *J Urol*, 2010. 184: 2498.
<https://www.ncbi.nlm.nih.gov/pubmed/20961572>
720. Bilen, C.Y., *et al.* Percutaneous nephrolithotomy in children: lessons learned in 5 years at a single institution. *J Urol*, 2007. 177: 1867.
<https://www.ncbi.nlm.nih.gov/pubmed/17437838>
721. Jackman, S.V., *et al.* The "mini-perc" technique: a less invasive alternative to percutaneous nephrolithotomy. *World J Urol*, 1998. 16: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/9870281>
722. Dede, O., *et al.* Ultra-mini-percutaneous nephrolithotomy in pediatric nephrolithiasis: Both low pressure and high efficiency. *J Pediatr Urol*, 2015. 11: 253 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/25964199>
723. Desai, M.R., *et al.* Single-step percutaneous nephrolithotomy (microperc): the initial clinical report. *J Urol*, 2011. 186: 140.
<https://www.ncbi.nlm.nih.gov/pubmed/21575966>
724. Hatipoglu, N.K., *et al.* Comparison of shockwave lithotripsy and microperc for treatment of kidney stones in children. *J Endourol*, 2013. 27: 1141.
<https://www.ncbi.nlm.nih.gov/pubmed/23713511>
725. Karatag, T., *et al.* A Comparison of 2 Percutaneous Nephrolithotomy Techniques for the Treatment of Pediatric Kidney Stones of Sizes 10-20 mm: Microperc vs Miniperc. *Urology*, 2015. 85: 1015.
<https://www.ncbi.nlm.nih.gov/pubmed/25917724>
726. Aghamir, S.M., *et al.* Feasibility of totally tubeless percutaneous nephrolithotomy under the age of 14 years: a randomized clinical trial. *J Endourol*, 2012. 26: 621.
<https://www.ncbi.nlm.nih.gov/pubmed/22192104>
727. Bodakci, M.N., *et al.* Ultrasound-guided micropercutaneous nephrolithotomy in pediatric patients with kidney stones. *Int J Urol*, 2015. 22: 773.
<https://www.ncbi.nlm.nih.gov/pubmed/25975519>
728. Gamal, W., *et al.* Supine pediatric percutaneous nephrolithotomy (PCNL). *J Pediatr Urol*, 2015. 11: 78 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/25819602>
729. Richter, S., *et al.* Early postureteroscopy vesicoureteral reflux--a temporary and infrequent complication: prospective study. *J Endourol*, 1999. 13: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/10446797>
730. Schuster, T.G., *et al.* Ureteroscopy for the treatment of urolithiasis in children. *J Urol*, 2002. 167: 1813.
<https://www.ncbi.nlm.nih.gov/pubmed/11912438>
731. al Busaidy, S.S., *et al.* Paediatric ureteroscopy for ureteric calculi: a 4-year experience. *Br J Urol*, 1997. 80: 797.
<https://www.ncbi.nlm.nih.gov/pubmed/9393306>
732. Hill, D.E., *et al.* Ureteroscopy in children. *J Urol*, 1990. 144: 481.
<https://www.ncbi.nlm.nih.gov/pubmed/2374224>
733. Gokce, M.I., *et al.* Evaluation of Postoperative Hydronephrosis Following Ureteroscopy in Pediatric Population: Incidence and Predictors. *Urology*, 2016. 93: 164.
<https://www.ncbi.nlm.nih.gov/pubmed/26972147>

734. Dogan, H.S., *et al.* Factors affecting complication rates of ureteroscopic lithotripsy in children: results of multi-institutional retrospective analysis by Pediatric Stone Disease Study Group of Turkish Pediatric Urology Society. *J Urol*, 2011. 186: 1035.
<https://www.ncbi.nlm.nih.gov/pubmed/24095906>
735. Abu Ghazaleh, L.A., *et al.* Retrograde intrarenal lithotripsy for small renal stones in prepubertal children. *Saudi J Kidney Dis Transpl*, 2011. 22: 492.
<https://www.ncbi.nlm.nih.gov/pubmed/21566306>
736. Corcoran, A.T., *et al.* When is prior ureteral stent placement necessary to access the upper urinary tract in prepubertal children? *J Urol*, 2008. 180: 1861.
<https://www.ncbi.nlm.nih.gov/pubmed/18721946>
737. Kim, S.S., *et al.* Pediatric flexible ureteroscopic lithotripsy: the children's hospital of Philadelphia experience. *J Urol*, 2008. 180: 2616.
<https://www.ncbi.nlm.nih.gov/pubmed/18950810>
738. Dave, S., *et al.* Single-institutional study on role of ureteroscopy and retrograde intrarenal surgery in treatment of pediatric renal calculi. *Urology*, 2008. 72: 1018.
<https://www.ncbi.nlm.nih.gov/pubmed/18585764>
739. Tanaka, S.T., *et al.* Pediatric ureteroscopic management of intrarenal calculi. *J Urol*, 2008. 180: 2150.
<https://www.ncbi.nlm.nih.gov/pubmed/18804225>
740. Erkurt, B., *et al.* Treatment of renal stones with flexible ureteroscopy in preschool age children. *Urolithiasis*, 2014. 42: 241.
<https://www.ncbi.nlm.nih.gov/pubmed/24374900>
741. Mokhless, I.A., *et al.* Retrograde intrarenal surgery monotherapy versus shock wave lithotripsy for stones 10 to 20 mm in preschool children: a prospective, randomized study. *J Urol*, 2014. 191: 1496.
<https://www.ncbi.nlm.nih.gov/pubmed/24679882>
742. Saad, K.S., *et al.* Percutaneous Nephrolithotomy vs Retrograde Intrarenal Surgery for Large Renal Stones in Pediatric Patients: A Randomized Controlled Trial. *J Urol*, 2015. 194: 1716.
<https://www.ncbi.nlm.nih.gov/pubmed/26165587>
743. Bas, O., *et al.* Comparison of Retrograde Intrarenal Surgery and Micro-Percutaneous Nephrolithotomy in Moderately Sized Pediatric Kidney Stones. *J Endourol*, 2016. 30: 765.
<https://www.ncbi.nlm.nih.gov/pubmed/26983791>
744. Lee, R.S., *et al.* Early results of robot assisted laparoscopic lithotomy in adolescents. *J Urol*, 2007. 177: 2306.
<https://www.ncbi.nlm.nih.gov/pubmed/17509345>
745. Casale, P., *et al.* Transperitoneal laparoscopic pyelolithotomy after failed percutaneous access in the pediatric patient. *J Urol*, 2004. 172: 680.
<https://www.ncbi.nlm.nih.gov/pubmed/15247760>
746. Ghani, K.R., *et al.* Robotic nephrolithotomy and pyelolithotomy with utilization of the robotic ultrasound probe. *Int Braz J Urol*, 2014. 40: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/24642160>
747. Srivastava, A., *et al.* Laparoscopic Ureterolithotomy in Children: With and Without Stent - Initial Tertiary Care Center Experience with More Than 1-Year Follow-Up. *Eur J Pediatr Surg*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/26878339>
748. Uson, A.C., *et al.* Ureteroceles in infants and children: a report based on 44 cases. *Pediatrics*, 1961. 27: 971.
<https://www.ncbi.nlm.nih.gov/pubmed/13779382>
749. Prewitt, L.H., Jr., *et al.* The single ectopic ureter. *AJR Am J Roentgenol*, 1976. 127: 941.
<https://www.ncbi.nlm.nih.gov/pubmed/998831>
750. Ahmed, S., *et al.* Single-system ectopic ureters: a review of 12 cases. *J Pediatr Surg*, 1992. 27: 491.
<https://www.ncbi.nlm.nih.gov/pubmed/1522464>
751. Chwalla, R. The process of formation of cystic dilatation of the vesical end of the ureter and of diverticula at the ureteral ostium. *Urol Cutan Ren* 1927. 31: 499. [No abstract available].
752. Tokunaka, S., *et al.* Muscle dysplasia in megaureters. *J Urol*, 1984. 131: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/6699978>
753. Stephens, D. Caecoureterocele and concepts on the embryology and aetiology of ureteroceles. *Aust N Z J Surg*, 1971. 40: 239.
<https://www.ncbi.nlm.nih.gov/pubmed/5279434>
754. Zerlin, J.M., *et al.* Single-system ureteroceles in infants and children: imaging features. *Pediatr Radiol*, 2000. 30: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/10755749>

755. Sen, S., *et al.* Single system ureterocele in childhood. *Aust N Z J Surg*, 1988. 58: 903.
<https://www.ncbi.nlm.nih.gov/pubmed/3074770>
756. Monfort, G., *et al.* Surgical management of duplex ureterocele. *J Pediatr Surg*, 1992. 27: 634.
<https://www.ncbi.nlm.nih.gov/pubmed/1625138>
757. Bolduc, S., *et al.* Histology of upper pole is unaffected by prenatal diagnosis in duplex system ureterocele. *J Urol*, 2002. 168: 1123.
<https://www.ncbi.nlm.nih.gov/pubmed/12187250>
758. Upadhyay, J., *et al.* Impact of prenatal diagnosis on the morbidity associated with ureterocele management. *J Urol*, 2002. 167: 2560.
<https://www.ncbi.nlm.nih.gov/pubmed/11992089>
759. Ellerker, A.G. The extravescical ectopic ureter. *Br J Surg*, 1958. 45: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/13536326>
760. Di Benedetto, V., *et al.* How prenatal ultrasound can change the treatment of ectopic ureterocele in neonates? *Eur J Pediatr Surg*, 1997. 7: 338.
<https://www.ncbi.nlm.nih.gov/pubmed/9493984>
761. Pfister, C., *et al.* The value of endoscopic treatment for ureterocele during the neonatal period. *J Urol*, 1998. 159: 1006.
<https://www.ncbi.nlm.nih.gov/pubmed/9474217>
762. Bozorgi, F., *et al.* Hypoplastic dysplastic kidney with a vaginal ectopic ureter identified by technetium-99m-DMSA scintigraphy. *J Nucl Med*, 1998. 39: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/9443748>
763. Connolly, L.P., *et al.* Ectopic ureterocele in infants with prenatal hydronephrosis: use of renal cortical scintigraphy. *Clin Nucl Med*, 2002. 27: 169.
<https://www.ncbi.nlm.nih.gov/pubmed/11852302>
764. Pattaras, J.G., *et al.* The role of 99mtechnetium dimercapto-succinic acid renal scans in the evaluation of occult ectopic ureters in girls with paradoxical incontinence. *J Urol*, 1999. 162: 821.
<https://www.ncbi.nlm.nih.gov/pubmed/10458388>
765. Meneghesso, D., *et al.* Clinico-pathological correlation in duplex system ectopic ureters and ureterocele: can preoperative work-up predict renal histology? *Pediatr Surg Int*, 2012. 28: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/22127487>
766. Bellah, R.D., *et al.* Ureterocele eversion with vesicoureteral reflux in duplex kidneys: findings at voiding cystourethrography. *AJR Am J Roentgenol*, 1995. 165: 409.
<https://www.ncbi.nlm.nih.gov/pubmed/7618568>
767. Carrico, C., *et al.* Incontinence due to an infrasphincteric ectopic ureter: why the delay in diagnosis and what the radiologist can do about it. *Pediatr Radiol*, 1998. 28: 942.
<https://www.ncbi.nlm.nih.gov/pubmed/9880638>
768. Ehammer, T., *et al.* High resolution MR for evaluation of lower urogenital tract malformations in infants and children: feasibility and preliminary experiences. *Eur J Radiol*, 2011. 78: 388.
<https://www.ncbi.nlm.nih.gov/pubmed/20138451>
769. Diard, F., *et al.* [Pseudo-ureterocele resulting from the impression of a loop of a megaureter with an ectopic subvesical orifice]. *J Radiol*, 1987. 68: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/3298636>
770. Sumfest, J.M., *et al.* Pseudoureterocele: potential for misdiagnosis of an ectopic ureter as a ureterocele. *Br J Urol*, 1995. 75: 401.
<https://www.ncbi.nlm.nih.gov/pubmed/7735809>
771. Figueroa, V.H., *et al.* Utility of MR urography in children suspected of having ectopic ureter. *Pediatr Radiol*, 2014. 44: 956.
<https://www.ncbi.nlm.nih.gov/pubmed/24535117>
772. Beganovic, A., *et al.* Ectopic ureterocele: long-term results of open surgical therapy in 54 patients. *J Urol*, 2007. 178: 251.
<https://www.ncbi.nlm.nih.gov/pubmed/17499769>
773. Byun, E., *et al.* A meta-analysis of surgical practice patterns in the endoscopic management of ureterocele. *J Urol*, 2006. 176: 1871.
<https://www.ncbi.nlm.nih.gov/pubmed/16945677>
774. Chertin, B., *et al.* Endoscopic treatment of vesicoureteral reflux associated with ureterocele. *J Urol*, 2007. 178: 1594.
<https://www.ncbi.nlm.nih.gov/pubmed/17707044>
775. Decter, R.M., *et al.* Individualized treatment of ureterocele. *J Urol*, 1989. 142: 535.
<https://www.ncbi.nlm.nih.gov/pubmed/2746775>

776. Husmann, D., *et al.* Management of ectopic ureterocele associated with renal duplication: a comparison of partial nephrectomy and endoscopic decompression. *J Urol*, 1999. 162: 1406.
<https://www.ncbi.nlm.nih.gov/pubmed/10492225>
777. Moscovici, J., *et al.* [Management of ureteroceles with pyelo-ureteral duplication in children. Report of 64 cases]. *Ann Urol (Paris)*, 1999. 33: 369.
<https://www.ncbi.nlm.nih.gov/pubmed/10544742>
778. Castagnetti, M., *et al.* Management of duplex system ureteroceles in neonates and infants. *Nat Rev Urol*, 2009. 6: 307.
<https://www.ncbi.nlm.nih.gov/pubmed/19498409>
779. Han, M.Y., *et al.* Indications for nonoperative management of ureteroceles. *J Urol*, 2005. 174: 1652.
<https://www.ncbi.nlm.nih.gov/pubmed/16148674>
780. Mariyappa, B., *et al.* Management of duplex-system ureterocele. *J Paediatr Child Health*, 2014. 50: 96.
<https://www.ncbi.nlm.nih.gov/pubmed/24372828>
781. Adorisio, O., *et al.* Effectiveness of primary endoscopic incision in treatment of ectopic ureterocele associated with duplex system. *Urology*, 2011. 77: 191.
<https://www.ncbi.nlm.nih.gov/pubmed/21168903>
782. DeFoor, W., *et al.* Ectopic ureterocele: clinical application of classification based on renal unit jeopardy. *J Urol*, 2003. 169: 1092.
<https://www.ncbi.nlm.nih.gov/pubmed/12576859>
783. Jayanthi, V.R., *et al.* Long-term outcome of transurethral puncture of ectopic ureteroceles: initial success and late problems. *J Urol*, 1999. 162: 1077.
<https://www.ncbi.nlm.nih.gov/pubmed/12187248>
784. Jesus, L.E., *et al.* Clinical evolution of vesicoureteral reflux following endoscopic puncture in children with duplex system ureteroceles. *J Urol*, 2011. 186: 1455.
<https://www.ncbi.nlm.nih.gov/pubmed/21862045>
785. Husmann, D.A., *et al.* Ureterocele associated with ureteral duplication and a nonfunctioning upper pole segment: management by partial nephroureterectomy alone. *J Urol*, 1995. 154: 723.
<https://www.ncbi.nlm.nih.gov/pubmed/7609163>
786. el Ghoneimi, A., *et al.* Ectopic ureter with complete ureteric duplication: conservative surgical management. *J Pediatr Surg*, 1996. 31: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/8801293>
787. Smith, F.L., *et al.* Surgery for duplex kidneys with ectopic ureters: ipsilateral ureteroureterostomy versus polar nephrectomy. *J Urol*, 1989. 142: 532.
<https://www.ncbi.nlm.nih.gov/pubmed/2746774>
788. Storm, D.W., *et al.* Laparoscopic ipsilateral ureteroureterostomy in the management of ureteral ectopia in infants and children. *J Pediatr Urol*, 2011. 7: 529.
<https://www.ncbi.nlm.nih.gov/pubmed/20869918>
789. Herndon, C.D., *et al.* A complex urologic problem demonstrates how far pediatric urology has progressed. *Conn Med*, 1999. 63: 707.
<https://www.ncbi.nlm.nih.gov/pubmed/10659470>
790. Jayanthi, V.R., *et al.* Bilateral single ureteral ectopia: difficulty attaining continence using standard bladder neck repair. *J Urol*, 1997. 158: 1933.
<https://www.ncbi.nlm.nih.gov/pubmed/9334642>
791. Johnin, K., *et al.* Bilateral single ectopic ureters with hypoplastic bladder: how should we treat these challenging entities? *J Pediatr Urol*, 2007. 3: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/18947744>
792. Roy Choudhury, S., *et al.* Spectrum of ectopic ureters in children. *Pediatr Surg Int*, 2008. 24: 819.
<https://www.ncbi.nlm.nih.gov/pubmed/18463883>
793. Lee, P.A., *et al.* Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics*, 2006. 118: e488.
<https://www.ncbi.nlm.nih.gov/pubmed/16882788>
794. Houk, C.P., *et al.* Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference. *Pediatrics*, 2006. 118: 753.
<https://www.ncbi.nlm.nih.gov/pubmed/16882833>
795. Maggi, M., *et al.* Standard operating procedures: pubertas tarda/delayed puberty--male. *J Sex Med*, 2013. 10: 285.
<https://www.ncbi.nlm.nih.gov/pubmed/22376050>
796. Wales, J.K. Disordered pubertal development. *Arch Dis Child Educ Pract Ed*, 2012. 97: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/21278425>

797. Feldman, K.W., *et al.* Fetal phallic growth and penile standards for newborn male infants. *J Pediatr*, 1975. 86: 395.
<https://www.ncbi.nlm.nih.gov/pubmed/1113226>
798. Aaronson, I.A. Micropenis: medical and surgical implications. *J Urol*, 1994. 152: 4.
<https://www.ncbi.nlm.nih.gov/pubmed/8201683>
799. Gonzales, J.R. Micropenis. *AUA Update Series*. 1983. 2. [No abstract available].
800. Choi, S.K., *et al.* Transdermal dihydrotestosterone therapy and its effects on patients with microphallus. *J Urol*, 1993. 150: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/8326617>
801. Burstein, S., *et al.* Early determination of androgen-responsiveness is important in the management of microphallus. *Lancet*, 1979. 2: 983.
<https://www.ncbi.nlm.nih.gov/pubmed/91775>
802. Diamond, M. Pediatric management of ambiguous and traumatized genitalia. *J Urol*, 1999. 162: 1021.
<https://www.ncbi.nlm.nih.gov/pubmed/10458424>
803. Bin-Abbas, B., *et al.* Congenital hypogonadotropic hypogonadism and micropenis: effect of testosterone treatment on adult penile size why sex reversal is not indicated. *J Pediatr*, 1999. 134: 579.
<https://www.ncbi.nlm.nih.gov/pubmed/10228293>
804. Calikoglu, A.S. Should boys with micropenis be reared as girls? *J Pediatr*, 1999. 134: 537.
<https://www.ncbi.nlm.nih.gov/pubmed/10228285>
805. Creighton, S., *et al.* Medical photography: ethics, consent and the intersex patient. *BJU Int*, 2002. 89: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/11849163>
806. Wright, N.B., *et al.* Imaging children with ambiguous genitalia and intersex states. *Clin Radiol*, 1995. 50: 823.
<https://www.ncbi.nlm.nih.gov/pubmed/8536391>
807. Biswas, K., *et al.* Imaging in intersex disorders. *J Pediatr Endocrinol Metab*, 2004. 17: 841.
<https://www.ncbi.nlm.nih.gov/pubmed/15270401>
808. Denes, F.T., *et al.* Laparoscopic management of intersexual states. *Urol Clin North Am*, 2001. 28: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/11277066>
809. Chertin, B., *et al.* The use of laparoscopy in intersex patients. *Pediatr Surg Int*, 2006. 22: 405.
<https://www.ncbi.nlm.nih.gov/pubmed/16521001>
810. Timing of elective surgery on the genitalia of male children with particular reference to the risks, benefits, and psychological effects of surgery and anesthesia. *American Academy of Pediatrics. Pediatrics*, 1996. 97: 590.
<http://pediatrics.aappublications.org/content/97/4/590>
811. Mouriquand, P., *et al.* The ESPU/SPU standpoint on the surgical management of Disorders of Sex Development (DSD). *J Pediatr Urol*, 2014. 10: 8.
<https://www.ncbi.nlm.nih.gov/pubmed/24528671>
812. Creighton, S.M. Adult female outcomes of feminising surgery for ambiguous genitalia. *Pediatr Endocrinol Rev*, 2004. 2: 199.
<https://www.ncbi.nlm.nih.gov/pubmed/16429106>
813. Minto, C.L., *et al.* The effect of clitoral surgery on sexual outcome in individuals who have intersex conditions with ambiguous genitalia: a cross-sectional study. *Lancet*, 2003. 361: 1252.
<https://www.ncbi.nlm.nih.gov/pubmed/12699952>
814. Crouch, N.S., *et al.* Minimal surgical intervention in the management of intersex conditions. *J Pediatr Endocrinol Metab*, 2004. 17: 1591.
<https://www.ncbi.nlm.nih.gov/pubmed/15645692>
815. Jenak, R., *et al.* Total urogenital sinus mobilization: a modified perineal approach for feminizing genitoplasty and urogenital sinus repair. *J Urol*, 2001. 165: 2347.
<https://www.ncbi.nlm.nih.gov/pubmed/11371975>
816. Leclair, M.D., *et al.* The surgical outcome of total urogenital mobilization for cloacal repair. *J Urol*, 2007. 177: 1492.
<https://www.ncbi.nlm.nih.gov/pubmed/17382761>
817. Schober, J.M. Feminizing genitoplasty: a synopsis of issues relating to genital surgery in intersex individuals. *J Pediatr Endocrinol Metab*, 2004. 17: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/15237702>

818. Cools, M., *et al.* Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. *Endocr Rev*, 2006. 27: 468.
<https://www.ncbi.nlm.nih.gov/pubmed/16735607>
819. Heikkila, J., *et al.* Long-term risk of end stage renal disease in patients with posterior urethral valves. *J Urol*, 2011. 186: 2392.
<https://www.ncbi.nlm.nih.gov/pubmed/22014822>
820. Reinberg, Y., *et al.* Influence of initial therapy on progression of renal failure and body growth in children with posterior urethral valves. *J Urol*, 1992. 148: 532.
<https://www.ncbi.nlm.nih.gov/pubmed/1640516>
821. Smith, G.H., *et al.* The long-term outcome of posterior urethral valves treated with primary valve ablation and observation. *J Urol*, 1996. 155: 1730.
<https://www.ncbi.nlm.nih.gov/pubmed/8627873>
822. Atwell, J.D. Posterior urethral valves in the British Isles: a multicenter B.A.P.S. review. *J Pediatr Surg*, 1983. 18: 70.
<https://www.ncbi.nlm.nih.gov/pubmed/6834230>
823. Casale, A.J. Early ureteral surgery for posterior urethral valves. *Urol Clin North Am*, 1990. 17: 361.
<https://www.ncbi.nlm.nih.gov/pubmed/2186541>
824. Cromie, W.J., *et al.* Implications of prenatal ultrasound screening in the incidence of major genitourinary malformations. *J Urol*, 2001. 165: 1677.
<https://www.ncbi.nlm.nih.gov/pubmed/11342955>
825. Dewan, P.A., *et al.* Endoscopic reappraisal of the morphology of congenital obstruction of the posterior urethra. *Br J Urol*, 1992. 70: 439.
<https://www.ncbi.nlm.nih.gov/pubmed/1450856>
826. Young, H.H., *et al.* Congenital obstruction of the posterior urethra. *J Urol*, 3: 289-365, 1919. *J Urol*, 2002. 167: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/11743334>
827. Rosenfeld, B., *et al.* Type III posterior urethral valves: presentation and management. *J Pediatr Surg*, 1994. 29: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/8120770>
828. Stephens, F.D., *et al.* Pathogenesis of the prune belly syndrome. *J Urol*, 1994. 152: 2328.
<https://www.ncbi.nlm.nih.gov/pubmed/7966734>
829. Bernardes, L.S., *et al.* Keyhole sign: how specific is it for the diagnosis of posterior urethral valves? *Ultrasound Obstet Gynecol*, 2009. 34: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/19642115>
830. Churchill, B.M., *et al.* Emergency treatment and long-term follow-up of posterior urethral valves. *Urol Clin North Am*, 1990. 17: 343.
<https://www.ncbi.nlm.nih.gov/pubmed/2186540>
831. Hoover, D.L., *et al.* Posterior urethral valves, unilateral reflux and renal dysplasia: a syndrome. *J Urol*, 1982. 128: 994.
<https://www.ncbi.nlm.nih.gov/pubmed/7176067>
832. Rittenberg, M.H., *et al.* Protective factors in posterior urethral valves. *J Urol*, 1988. 140: 993.
<https://www.ncbi.nlm.nih.gov/pubmed/3139895>
833. Cuckow, P.M., *et al.* Long-term renal function in the posterior urethral valves, unilateral reflux and renal dysplasia syndrome. *J Urol*, 1997. 158: 1004.
<https://www.ncbi.nlm.nih.gov/pubmed/9258130>
834. Kleppe, S., *et al.* Impact of prenatal urinomas in patients with posterior urethral valves and postnatal renal function. *J Perinat Med*, 2006. 34: 425.
<https://www.ncbi.nlm.nih.gov/pubmed/16965232>
835. Dinneen, M.D., *et al.* Antenatal diagnosis of posterior urethral valves. *Br J Urol*, 1993. 72: 364.
<https://www.ncbi.nlm.nih.gov/pubmed/8220998>
836. Freedman, A.L., *et al.* Fetal therapy for obstructive uropathy: past, present, future? *Pediatr Nephrol*, 2000. 14: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/10684370>
837. McLorie, G., *et al.* Outcome analysis of vesicoamniotic shunting in a comprehensive population. *J Urol*, 2001. 166: 1036.
<https://www.ncbi.nlm.nih.gov/pubmed/11490292>
838. Salam, M.A. Posterior urethral valve: Outcome of antenatal intervention. *Int J Urol*, 2006. 13: 1317.
<https://www.ncbi.nlm.nih.gov/pubmed/17010011>

839. Morris, R.K., *et al.* Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. *Lancet*, 2013. 382: 1496.
<https://www.ncbi.nlm.nih.gov/pubmed/23953766>
840. Morris, R.K., *et al.* A systematic review and meta-analysis of the effectiveness of fetal cystoscopy as an intervention for congenital bladder neck obstruction. *Repr Sciences* 2011. 18: 366A.
http://fn.bmj.com/content/96/Suppl_1/Fa61.2.abstract
841. Martinez, J.M., *et al.* Laser ablation of posterior urethral valves by fetal cystoscopy. *Fetal Diagn Ther*, 2015. 37: 267.
<https://www.ncbi.nlm.nih.gov/pubmed/25614247>
842. Babu, R., *et al.* Early outcome following diathermy versus cold knife ablation of posterior urethral valves. *J Pediatr Urol*, 2013. 9: 7.
<https://www.ncbi.nlm.nih.gov/pubmed/22417679>
843. Shirazi, M., *et al.* Which patients are at higher risk for residual valves after posterior urethral valve ablation? *Korean J Urol*, 2014. 55: 64.
<https://www.ncbi.nlm.nih.gov/pubmed/24466400>
844. Krahn, C.G., *et al.* Cutaneous vesicostomy in the young child: indications and results. *Urology*, 1993. 41: 558.
<https://www.ncbi.nlm.nih.gov/pubmed/8516992>
845. Kim, Y.H., *et al.* Comparative urodynamic findings after primary valve ablation, vesicostomy or proximal diversion. *J Urol*, 1996. 156: 673.
<https://www.ncbi.nlm.nih.gov/pubmed/8683757>
846. Podesta, M., *et al.* Bladder function associated with posterior urethral valves after primary valve ablation or proximal urinary diversion in children and adolescents. *J Urol*, 2002. 168: 1830.
<https://www.ncbi.nlm.nih.gov/pubmed/12352370>
847. Novak, M.E., *et al.* Single-stage reconstruction of urinary tract after loop cutaneous ureterostomy. *Urology*, 1978. 11: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/628990>
848. Sober, I. Pelvioureterostomy-en-Y. *J Urol*, 1972. 107: 473.
<https://www.ncbi.nlm.nih.gov/pubmed/5010719>
849. Williams, D.I., *et al.* Ring ureterostomy. *Br J Urol*, 1975. 47: 789.
<https://www.ncbi.nlm.nih.gov/pubmed/1222345>
850. Scott, J.E. Management of congenital posterior urethral valves. *Br J Urol*, 1985. 57: 71.
<https://www.ncbi.nlm.nih.gov/pubmed/3971107>
851. Mukherjee, S., *et al.* What is the effect of circumcision on risk of urinary tract infection in boys with posterior urethral valves? *J Pediatr Surg*, 2009. 44: 417.
<https://www.ncbi.nlm.nih.gov/pubmed/19231547>
852. Cozzi, D.A., *et al.* Posterior urethral valves: relationship between vesicoureteral reflux and renal function. *Urology*, 2011. 77: 1209.
<https://www.ncbi.nlm.nih.gov/pubmed/21109298>
853. Bellinger, M.F. Ureterocystoplasty: a unique method for vesical augmentation in children. *J Urol*, 1993. 149: 811.
<https://www.ncbi.nlm.nih.gov/pubmed/8455246>
854. Misseri, R., *et al.* Myogenic failure in posterior urethral valve disease: real or imagined? *J Urol*, 2002. 168: 1844.
<https://www.ncbi.nlm.nih.gov/pubmed/12352373>
855. Kim, Y.H., *et al.* Management of posterior urethral valves on the basis of urodynamic findings. *J Urol*, 1997. 158: 1011.
<https://www.ncbi.nlm.nih.gov/pubmed/9258132>
856. Abraham, M.K., *et al.* Role of alpha adrenergic blocker in the management of posterior urethral valves. *Pediatr Surg Int*, 2009. 25: 1113.
<https://www.ncbi.nlm.nih.gov/pubmed/19727771>
857. Skenazy, J., *et al.* 1618 Alpha adrenergic blockade in neonates with posterior urethral valves. *J Urol*, 2012. 187: e654.
<http://www.sciencedirect.com/science/article/pii/S0022534712017752>
858. DeFoor, W., *et al.* Risk factors for end stage renal disease in children with posterior urethral valves. *J Urol*, 2008. 180: 1705.
<https://www.ncbi.nlm.nih.gov/pubmed/18708224>
859. Kamal, M.M., *et al.* Impact of posterior urethral valves on pediatric renal transplantation: a single-center comparative study of 297 cases. *Pediatr Transplant*, 2011. 15: 482.
<https://www.ncbi.nlm.nih.gov/pubmed/21599816>

860. Fine, M.S., *et al.* Posterior urethral valve treatments and outcomes in children receiving kidney transplants. *J Urol*, 2011. 185: 2507.
<https://www.ncbi.nlm.nih.gov/pubmed/21527196>
861. Salomon, L., *et al.* Role of the bladder in delayed failure of kidney transplants in boys with posterior urethral valves. *J Urol*, 2000. 163: 1282.
<https://www.ncbi.nlm.nih.gov/pubmed/10737529>
862. McAninch, J.W., *et al.* Renal reconstruction after injury. *J Urol*, 1991. 145: 932.
<https://www.ncbi.nlm.nih.gov/pubmed/2016804>
863. McAleer, I.M., *et al.* Genitourinary trauma in the pediatric patient. *Urology*, 1993. 42: 563.
<https://www.ncbi.nlm.nih.gov/pubmed/8236601>
864. Miller, R.C., *et al.* The incidental discovery of occult abdominal tumors in children following blunt abdominal trauma. *J Trauma*, 1966. 6: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/5901856>
865. Moore, E.E., *et al.* Organ injury scaling: spleen, liver, and kidney. *J Trauma*, 1989. 29: 1664.
<https://www.ncbi.nlm.nih.gov/pubmed/2593197>
866. Stalker, H.P., *et al.* The significance of hematuria in children after blunt abdominal trauma. *AJR Am J Roentgenol*, 1990. 154: 569.
<https://www.ncbi.nlm.nih.gov/pubmed/2106223>
867. Mee, S.L., *et al.* Radiographic assessment of renal trauma: a 10-year prospective study of patient selection. *J Urol*, 1989. 141: 1095.
<https://www.ncbi.nlm.nih.gov/pubmed/2709493>
868. Stein, J.P., *et al.* Blunt renal trauma in the pediatric population: indications for radiographic evaluation. *Urology*, 1994. 44: 406.
<https://www.ncbi.nlm.nih.gov/pubmed/8073555>
869. Carpio, F., *et al.* Radiographic staging of renal injuries. *World J Urol*, 1999. 17: 66.
<https://www.ncbi.nlm.nih.gov/pubmed/10367363>
870. Radmayr, C., *et al.* Blunt renal trauma in children: 26 years clinical experience in an alpine region. *Eur Urol*, 2002. 42: 297.
<https://www.ncbi.nlm.nih.gov/pubmed/12234516>
871. Presti, J.C., Jr., *et al.* Ureteral and renal pelvic injuries from external trauma: diagnosis and management. *J Trauma*, 1989. 29: 370.
<https://www.ncbi.nlm.nih.gov/pubmed/2926851>
872. Mulligan, J.M., *et al.* Ureteropelvic junction disruption secondary to blunt trauma: excretory phase imaging (delayed films) should help prevent a missed diagnosis. *J Urol*, 1998. 159: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/9400439>
873. al-Ali, M., *et al.* The late treatment of 63 overlooked or complicated ureteral missile injuries: the promise of nephrostomy and role of autotransplantation. *J Urol*, 1996. 156: 1918.
<https://www.ncbi.nlm.nih.gov/pubmed/8911355>
874. Fernandez Fernandez, A., *et al.* Blunt traumatic rupture of the high right ureter, repaired with appendix interposition. *Urol Int*, 1994. 53: 97.
<https://www.ncbi.nlm.nih.gov/pubmed/7801425>
875. Sivit, C.J., *et al.* CT diagnosis and localization of rupture of the bladder in children with blunt abdominal trauma: significance of contrast material extravasation in the pelvis. *AJR Am J Roentgenol*, 1995. 164: 1243.
<https://www.ncbi.nlm.nih.gov/pubmed/7717239>
876. Hochberg, E., *et al.* Bladder rupture associated with pelvic fracture due to blunt trauma. *Urology*, 1993. 41: 531.
<https://www.ncbi.nlm.nih.gov/pubmed/8516988>
877. Haas, C.A., *et al.* Limitations of routine spiral computerized tomography in the evaluation of bladder trauma. *J Urol*, 1999. 162: 51.
<https://www.ncbi.nlm.nih.gov/pubmed/10379738>
878. Volpe, M.A., *et al.* Is there a difference in outcome when treating traumatic intraperitoneal bladder rupture with or without a suprapubic tube? *J Urol*, 1999. 161: 1103.
<https://www.ncbi.nlm.nih.gov/pubmed/10081847>
879. Richardson, J.R., Jr., *et al.* Non-operative treatment of the ruptured bladder. *J Urol*, 1975. 114: 213.
<https://www.ncbi.nlm.nih.gov/pubmed/1159910>
880. Cass, A.S., *et al.* Urethral injury due to external trauma. *Urology*, 1978. 11: 607.
<https://www.ncbi.nlm.nih.gov/pubmed/675928>
881. Pokorny, M., *et al.* Urological injuries associated with pelvic trauma. *J Urol*, 1979. 121: 455.
<https://www.ncbi.nlm.nih.gov/pubmed/439217>

882. Elliott, D.S., *et al.* Long-term followup and evaluation of primary realignment of posterior urethral disruptions. *J Urol*, 1997. 157: 814.
<https://www.ncbi.nlm.nih.gov/pubmed/9072573>
883. Boone, T.B., *et al.* Postpubertal genitourinary function following posterior urethral disruptions in children. *J Urol*, 1992. 148: 1232.
<https://www.ncbi.nlm.nih.gov/pubmed/1404642>
884. Koraitim, M.M. Posttraumatic posterior urethral strictures in children: a 20-year experience. *J Urol*, 1997. 157: 641.
<https://www.ncbi.nlm.nih.gov/pubmed/8996388>
885. Avanoğlu, A., *et al.* Posterior urethral injuries in children. *Br J Urol*, 1996. 77: 597.
<https://www.ncbi.nlm.nih.gov/pubmed/8777627>
886. Nair, S.G., *et al.* Perioperative fluid and electrolyte management in pediatric patients. *Indian J Anaesth*, 2004. 48: 355.
<http://medind.nic.in/iadt/t04/i5/iadt04i5p355.pdf>
887. Imura, K., *et al.* Perioperative nutrition and metabolism in pediatric patients. *World J Surg*, 2000. 24: 1498.
<https://www.ncbi.nlm.nih.gov/pubmed/11193714>
888. Ward Platt, M.P., *et al.* The effects of anesthesia and surgery on metabolic homeostasis in infancy and childhood. *J Pediatr Surg*, 1990. 25: 472.
<https://www.ncbi.nlm.nih.gov/pubmed/2191106>
889. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: a report by the American Society of Anesthesiologist Task Force on Preoperative Fasting. *Anesthesiology*, 1999. 90: 896.
<https://www.ncbi.nlm.nih.gov/pubmed/10078693>
890. Murat, I., *et al.* Perioperative fluid therapy in pediatrics. *Paediatr Anaesth*, 2008. 18: 363.
<https://www.ncbi.nlm.nih.gov/pubmed/18312509>
891. Redfern, N., *et al.* Blood glucose in anaesthetised children. Comparison of blood glucose concentrations in children fasted for morning and afternoon surgery. *Anaesthesia*, 1986. 41: 272.
<https://www.ncbi.nlm.nih.gov/pubmed/3963330>
892. Leelanukrom, R., *et al.* Intraoperative fluid and glucose management in children. *Paediatr Anaesth*, 2000. 10: 353.
<https://www.ncbi.nlm.nih.gov/pubmed/10886690>
893. Holliday, M.A., *et al.* The maintenance need for water in parenteral fluid therapy. *Pediatrics*, 1957. 19: 823.
<https://www.ncbi.nlm.nih.gov/pubmed/13431307>
894. Lindahl, S.G. Energy expenditure and fluid and electrolyte requirements in anesthetized infants and children. *Anesthesiology*, 1988. 69: 377.
<https://www.ncbi.nlm.nih.gov/pubmed/3415017>
895. Bailey, A.G., *et al.* Perioperative crystalloid and colloid fluid management in children: where are we and how did we get here? *Anesth Analg*, 2010. 110: 375.
<https://www.ncbi.nlm.nih.gov/pubmed/19955503>
896. Furman, E.B., *et al.* Specific therapy in water, electrolyte and blood-volume replacement during pediatric surgery. *Anesthesiology*, 1975. 42: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/1115368>
897. Berry, F., *Practical aspects of fluid and electrolyte therapy*, in *Anesthetic Management of Difficult and Routine Pediatric Patients*, 1986, Churchill Livingstone: New York.
898. Kearney, R., *et al.* Withholding oral fluids from children undergoing day surgery reduces vomiting. *Paediatr Anaesth*, 1998. 8: 331.
<https://www.ncbi.nlm.nih.gov/pubmed/9672932>
899. Goodarzi, M., *et al.* A prospective randomized blinded study of the effect of intravenous fluid therapy on postoperative nausea and vomiting in children undergoing strabismus surgery. *Paediatr Anaesth*, 2006. 16: 49.
<https://www.ncbi.nlm.nih.gov/pubmed/16409529>
900. Moritz, M.L., *et al.* Intravenous fluid management for the acutely ill child. *Curr Opin Pediatr*, 2011. 23: 186.
<https://www.ncbi.nlm.nih.gov/pubmed/21415832>
901. Yung, M., *et al.* Randomised controlled trial of intravenous maintenance fluids. *J Paediatr Child Health*, 2009. 45: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/18036144>

902. Duke, T., *et al.* Intravenous fluids for seriously ill children: time to reconsider. *Lancet*, 2003. 362: 1320.
<https://www.ncbi.nlm.nih.gov/pubmed/14575980>
903. Greenbaum, L., The pathophysiology of body fluids and fluid therapy, in Kliegman: Nelson textbook of pediatrics, 2007, Saunders Elsevier: Philadelphia, PA.
904. Holliday, M.A., *et al.* Fluid therapy for children: facts, fashions and questions. *Arch Dis Child*, 2007. 92: 546.
<https://www.ncbi.nlm.nih.gov/pubmed/17175577>
905. Moritz, M.L., *et al.* Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. *Pediatrics*, 2003. 111: 227.
<https://www.ncbi.nlm.nih.gov/pubmed/12563043>
906. Messner, A.H., *et al.* Oral fluid intake following tonsillectomy. *Int J Pediatr Otorhinolaryngol*, 1997. 39: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/9051436>
907. Schreiner, M.S., *et al.* Should children drink before discharge from day surgery? *Anesthesiology*, 1992. 76: 528.
<https://www.ncbi.nlm.nih.gov/pubmed/1550277>
908. Radke, O.C., *et al.* The effect of postoperative fasting on vomiting in children and their assessment of pain. *Paediatr Anaesth*, 2009. 19: 494.
<https://www.ncbi.nlm.nih.gov/pubmed/19453581>
909. Cheng, W., *et al.* Electrogastrographic changes in children who undergo day-surgery anesthesia. *J Pediatr Surg*, 1999. 34: 1336.
<https://www.ncbi.nlm.nih.gov/pubmed/10507424>
910. Mercan, A., *et al.* The effect of timing and temperature of oral fluids ingested after minor surgery in preschool children on vomiting: a prospective, randomized, clinical study. *Paediatr Anaesth*, 2011. 21: 1066.
<https://www.ncbi.nlm.nih.gov/pubmed/21668799>
911. Everett, L.L. Pain management for pediatric ambulatory anesthesia. *Curr Opin Anaesthesiol*, 2002. 15: 609.
<https://www.ncbi.nlm.nih.gov/pubmed/17019260>
912. Bozkurt, P. The analgesic efficacy and neuroendocrine response in paediatric patients treated with two analgesic techniques: using morphine-epidural and patient-controlled analgesia. *Paediatr Anaesth*, 2002. 12: 248.
<https://www.ncbi.nlm.nih.gov/pubmed/11903939>
913. Gehdoo, R.P. Postoperative pain management in pediatric patients. *Indian J Anesth* 2004. 48: 406.
<http://medind.nic.in/iad/t04/i5/iadt04i5p406.pdf>
914. Arana, A., *et al.* Treatment with paracetamol in infants. *Acta Anaesthesiol Scand*, 2001. 45: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/11152028>
915. Messerer, B., *et al.* Implementation of a standardized pain management in a pediatric surgery unit. *Pediatr Surg Int*, 2010. 26: 879.
<https://www.ncbi.nlm.nih.gov/pubmed/20625751>
916. Vergheze, S.T., *et al.* Acute pain management in children. *J Pain Res*, 2010. 3: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/21197314>
917. Ivani, G., *et al.* Postoperative analgesia in infants and children: new developments. *Minerva Anesthesiol*, 2004. 70: 399.
<https://www.ncbi.nlm.nih.gov/pubmed/15181422>
918. Karling, M., *et al.* Acute and postoperative pain in children: a Swedish nationwide survey. *Acta Paediatr*, 2002. 91: 660.
<https://www.ncbi.nlm.nih.gov/pubmed/12162598>
919. Stamer, U.M., *et al.* Postoperative analgesia in children--current practice in Germany. *Eur J Pain*, 2005. 9: 555.
<https://www.ncbi.nlm.nih.gov/pubmed/16139184>
920. Taylor, B.J., *et al.* Assessing postoperative pain in neonates: a multicenter observational study. *Pediatrics*, 2006. 118: e992.
<https://www.ncbi.nlm.nih.gov/pubmed/17015519>
921. Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. *Pediatrics*, 2000. 105: 454.
<https://www.ncbi.nlm.nih.gov/pubmed/10654977>

922. Anand, K.J. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med*, 2001. 155: 173.
<https://www.ncbi.nlm.nih.gov/pubmed/11177093>
923. Simons, S.H., *et al.* Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Arch Pediatr Adolesc Med*, 2003. 157: 1058.
<https://www.ncbi.nlm.nih.gov/pubmed/14609893>
924. Taddio, A., *et al.* Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet*, 1997. 349: 599.
<https://www.ncbi.nlm.nih.gov/pubmed/9057731>
925. Grunau, R.E., *et al.* Demographic and therapeutic determinants of pain reactivity in very low birth weight neonates at 32 Weeks' postconceptional Age. *Pediatrics*, 2001. 107: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/11134442>
926. Kain, Z.N., *et al.* Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. *Pediatrics*, 2006. 118: 651.
<https://www.ncbi.nlm.nih.gov/pubmed/16882820>
927. Young, K.D. Pediatric procedural pain. *Ann Emerg Med*, 2005. 45: 160.
<https://www.ncbi.nlm.nih.gov/pubmed/15671974>
928. Ghai, B., *et al.* Postoperative pain assessment in preverbal children and children with cognitive impairment. *Paediatr Anaesth*, 2008. 18: 462.
<https://www.ncbi.nlm.nih.gov/pubmed/18363630>
929. Ellis, J.A., *et al.* Evaluation of a continuous epidural analgesia program for postoperative pain in children. *Pain Manag Nurs*, 2007. 8: 146.
<https://www.ncbi.nlm.nih.gov/pubmed/18036502>
930. Schechter, W.P., *et al.* Special considerations in perioperative pain management: audiovisual distraction, geriatrics, pediatrics, and pregnancy. *J Am Coll Surg*, 2005. 201: 612.
<https://www.ncbi.nlm.nih.gov/pubmed/16183502>
931. Jonas, D.A. Parent's management of their child's pain in the home following day surgery. *J Child Health Care*, 2003. 7: 150.
<https://www.ncbi.nlm.nih.gov/pubmed/14516009>
932. Kankkunen, P., *et al.* Families' and children's postoperative pain--literature review. *J Pediatr Nurs*, 2004. 19: 133.
<https://www.ncbi.nlm.nih.gov/pubmed/15077212>
933. Birmingham, P.K., *et al.* Patient-controlled epidural analgesia in children: can they do it? *Anesth Analg*, 2003. 96: 686.
<https://www.ncbi.nlm.nih.gov/pubmed/12598244>
934. Woolf, C.J., *et al.* Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg*, 1993. 77: 362.
<https://www.ncbi.nlm.nih.gov/pubmed/8346839>
935. Kehlet, H., *et al.* The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg*, 1993. 77: 1048.
<https://www.ncbi.nlm.nih.gov/pubmed/8105724>
936. World Health Organization, Cancer Pain Relief and Palliative Care in Children. 1998, World Health Organization: Geneva.
<http://apps.who.int/iris/bitstream/10665/42001/1/9241545127.pdf>
937. Anand, K.J., *et al.* Analgesia and local anesthesia during invasive procedures in the neonate. *Clin Ther*, 2005. 27: 844.
<https://www.ncbi.nlm.nih.gov/pubmed/16117989>
938. Yawman, D., *et al.* Pain relief for neonatal circumcision: a follow-up of residency training practices. *Ambul Pediatr*, 2006. 6: 210.
<https://www.ncbi.nlm.nih.gov/pubmed/16843252>
939. Choi, W.Y., *et al.* EMLA cream versus dorsal penile nerve block for postcircumcision analgesia in children. *Anesth Analg*, 2003. 96: 396.
<https://www.ncbi.nlm.nih.gov/pubmed/12538184>
940. Lehr, V.T., *et al.* Lidocaine 4% cream compared with lidocaine 2.5% and prilocaine 2.5% or dorsal penile block for circumcision. *Am J Perinatol*, 2005. 22: 231.
<https://www.ncbi.nlm.nih.gov/pubmed/16041631>
941. Matsota, P., *et al.* Intraoperative and postoperative analgesia with subcutaneous ring block of the penis with levobupivacaine for circumcision in children. *Eur J Pediatr Surg*, 2004. 14: 198.
<https://www.ncbi.nlm.nih.gov/pubmed/15211412>

942. Smith, D.P., *et al.* The efficacy of LMX versus EMLA for pain relief in boys undergoing office meatotomy. *J Urol*, 2004. 172: 1760.
<https://www.ncbi.nlm.nih.gov/pubmed/15371808>
943. Taddio, A., *et al.* A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. *Pediatrics*, 1998. 101: E1.
<https://www.ncbi.nlm.nih.gov/pubmed/9445511>
944. Brady-Fryer, B., *et al.* Pain relief for neonatal circumcision. *Cochrane Database Syst Rev*, 2004: CD004217.
<https://www.ncbi.nlm.nih.gov/pubmed/15495086>
945. Sandeman, D.J., *et al.* A retrospective audit of three different regional anaesthetic techniques for circumcision in children. *Anaesth Intensive Care*, 2010. 38: 519.
<https://www.ncbi.nlm.nih.gov/pubmed/20514962>
946. Faraoni, D., *et al.* Does ultrasound guidance improve the efficacy of dorsal penile nerve block in children? *Paediatr Anaesth*, 2010. 20: 931.
<https://www.ncbi.nlm.nih.gov/pubmed/20849498>
947. Cyna, A.M., *et al.* Caudal epidural block versus other methods of postoperative pain relief for circumcision in boys. *Cochrane Database Syst Rev*, 2008: CD003005.
<https://www.ncbi.nlm.nih.gov/pubmed/18843636>
948. Margetts, L., *et al.* A comparison of caudal bupivacaine and ketamine with penile block for paediatric circumcision. *Eur J Anaesthesiol*, 2008. 25: 1009.
<https://www.ncbi.nlm.nih.gov/pubmed/18652709>
949. Weksler, N., *et al.* Is penile block better than caudal epidural block for postcircumcision analgesia? *J Anesth*, 2005. 19: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/>
950. Gauntlett, I. A comparison between local anaesthetic dorsal nerve block and caudal bupivacaine with ketamine for paediatric circumcision. *Paediatr Anaesth*, 2003. 13: 38.
<https://www.ncbi.nlm.nih.gov/pubmed/12535037>
951. Sharpe, P., *et al.* Analgesia for circumcision in a paediatric population: comparison of caudal bupivacaine alone with bupivacaine plus two doses of clonidine. *Paediatr Anaesth*, 2001. 11: 695.
<https://www.ncbi.nlm.nih.gov/pubmed/11696146>
952. Beyaz, S.G. Comparison of Postoperative Analgesic Efficacy of Caudal Block versus Dorsal Penile Nerve Block with Levobupivacaine for Circumcision in Children. *Korean J Pain*, 2011. 24: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/21390176>
953. Al-Zaben, K.R., *et al.* Intraoperative administration of dexmedetomidine reduces the analgesic requirements for children undergoing hypospadias surgery. *Eur J Anaesthesiol*, 2010. 27: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/19952754>
954. Cho, J.E., *et al.* The addition of fentanyl to 1.5 mg/ml ropivacaine has no advantage for paediatric epidural analgesia. *Acta Anaesthesiol Scand*, 2009. 53: 1084.
<https://www.ncbi.nlm.nih.gov/pubmed/19572930>
955. Gunduz, M., *et al.* Comparison of caudal ketamine with lidocaine or tramadol administration for postoperative analgesia of hypospadias surgery in children. *Paediatr Anaesth*, 2006. 16: 158.
<https://www.ncbi.nlm.nih.gov/pubmed/16430412>
956. Silvani, P., *et al.* Caudal anesthesia in pediatrics: an update. *Minerva Anesthesiol*, 2006. 72: 453.
<https://www.ncbi.nlm.nih.gov/pubmed/16682915>
957. Apiliogullari, S., *et al.* Efficacy of a low-dose spinal morphine with bupivacaine for postoperative analgesia in children undergoing hypospadias repair. *Paediatr Anaesth*, 2009. 19: 1078.
<https://www.ncbi.nlm.nih.gov/pubmed/19708911>
958. Laiq, N., *et al.* Comparison of caudal bupivacaine and bupivacaine-tramadol for postoperative analgesia in children undergoing hypospadias surgery. *J Coll Physicians Surg Pak*, 2009. 19: 678.
<https://www.ncbi.nlm.nih.gov/pubmed/19889260>
959. Gunes, Y., *et al.* Comparison of caudal vs intravenous tramadol administered either preoperatively or postoperatively for pain relief in boys. *Paediatr Anaesth*, 2004. 14: 324.
<https://www.ncbi.nlm.nih.gov/pubmed/15078378>
960. Hansen, T.G., *et al.* Caudal bupivacaine supplemented with caudal or intravenous clonidine in children undergoing hypospadias repair: a double-blind study. *Br J Anaesth*, 2004. 92: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/14722172>
961. Thies, K.C., *et al.* Longer than expected-duration of caudal analgesia with two different doses of levobupivacaine in children undergoing hypospadias repair. *J Pediatr Urol*, 2010. 6: 585.
<https://www.ncbi.nlm.nih.gov/pubmed/20171143>

962. De Negri, P., *et al.* A comparison of epidural bupivacaine, levobupivacaine, and ropivacaine on postoperative analgesia and motor blockade. *Anesth Analg*, 2004. 99: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/15281501>
963. Ozbek, H., *et al.* The comparison of caudal ketamine, alfentanil and ketamine plus alfentanil administration for postoperative analgesia in children. *Paediatr Anaesth*, 2002. 12: 610.
<https://www.ncbi.nlm.nih.gov/pubmed/12358657>
964. Bhardwaj, N., *et al.* Neostigmine does not prolong the duration of analgesia produced by caudal bupivacaine in children undergoing urethroplasty. *J Postgrad Med*, 2007. 53: 161.
<https://www.ncbi.nlm.nih.gov/pubmed/17699988>
965. Ozyuvaci, E., *et al.* Evaluation of adding preoperative or postoperative rectal paracetamol to caudal bupivacaine for postoperative analgesia in children. *Paediatr Anaesth*, 2004. 14: 661.
<https://www.ncbi.nlm.nih.gov/pubmed/15283825>
966. Samuel, M., *et al.* Prospective to a randomized double-blind controlled trial to assess efficacy of double caudal analgesia in hypospadias repair. *J Pediatr Surg*, 2002. 37: 168.
<https://www.ncbi.nlm.nih.gov/pubmed/11819193>
967. Abdulatif, M., *et al.* Caudal neostigmine, bupivacaine, and their combination for postoperative pain management after hypospadias surgery in children. *Anesth Analg*, 2002. 95: 1215.
<https://www.ncbi.nlm.nih.gov/pubmed/12401596>
968. Metzelder, M.L., *et al.* Penile block is associated with less urinary retention than caudal anesthesia in distal hypospadias repair in children. *World J Urol*, 2010. 28: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/19466428>
969. Chhibber, A.K., *et al.* Penile block timing for postoperative analgesia of hypospadias repair in children. *J Urol*, 1997. 158: 1156.
<https://www.ncbi.nlm.nih.gov/pubmed/9258161>
970. Breschan, C., *et al.* A prospective study comparing the analgesic efficacy of levobupivacaine, ropivacaine and bupivacaine in pediatric patients undergoing caudal blockade. *Paediatr Anaesth*, 2005. 15: 301.
<https://www.ncbi.nlm.nih.gov/pubmed/15787921>
971. Hong, J.Y., *et al.* Effect of dexamethasone in combination with caudal analgesia on postoperative pain control in day-case paediatric orchiopey. *Br J Anaesth*, 2010. 105: 506.
<https://www.ncbi.nlm.nih.gov/pubmed/20659915>
972. Taheri, R., *et al.* Efficacy of bupivacaine-neostigmine and bupivacaine-tramadol in caudal block in pediatric inguinal herniorrhaphy. *Paediatr Anaesth*, 2010. 20: 866.
<https://www.ncbi.nlm.nih.gov/pubmed/20716080>
973. Fredrickson, M.J., *et al.* Improved analgesia with the ilioinguinal block compared to the transversus abdominis plane block after pediatric inguinal surgery: a prospective randomized trial. *Paediatr Anaesth*, 2010. 20: 1022.
<https://www.ncbi.nlm.nih.gov/pubmed/20964768>
974. Jagannathan, N., *et al.* Unilateral groin surgery in children: will the addition of an ultrasound-guided ilioinguinal nerve block enhance the duration of analgesia of a single-shot caudal block? *Paediatr Anaesth*, 2009. 19: 892.
<https://www.ncbi.nlm.nih.gov/pubmed/19627532>
975. Demiraran, Y., *et al.* Does tramadol wound infiltration offer an advantage over bupivacaine for postoperative analgesia in children following herniotomy? *Paediatr Anaesth*, 2006. 16: 1047.
<https://www.ncbi.nlm.nih.gov/pubmed/16972834>
976. Machotta, A., *et al.* Comparison between instillation of bupivacaine versus caudal analgesia for postoperative analgesia following inguinal herniotomy in children. *Paediatr Anaesth*, 2003. 13: 397.
<https://www.ncbi.nlm.nih.gov/pubmed/12791112>
977. Shenfeld, O., *et al.* Intraoperative irrigation with bupivacaine for analgesia after orchiopey and herniorrhaphy in children. *J Urol*, 1995. 153: 185.
<https://www.ncbi.nlm.nih.gov/pubmed/7966769>
978. Saeed, A., *et al.* Pain management for unilateral orchidopexy in children: an effective regimen. *World J Surg*, 2009. 33: 603.
<https://www.ncbi.nlm.nih.gov/pubmed/19115030>
979. Tripi, P.A., *et al.* Clonidine increases duration of bupivacaine caudal analgesia for ureteroneocystostomy: a double-blind prospective trial. *J Urol*, 2005. 174: 1081.
<https://www.ncbi.nlm.nih.gov/pubmed/16094063>
980. Merguerian, P.A., *et al.* Efficacy of continuous epidural analgesia versus single dose caudal analgesia in children after intravesical ureteroneocystostomy. *J Urol*, 2004. 172: 1621.
<https://www.ncbi.nlm.nih.gov/pubmed/15371775>

981. Cain, M.P., *et al.* Continuous epidural anesthesia after ureteroneocystostomy in children. *J Urol*, 1995. 154: 791.
<https://www.ncbi.nlm.nih.gov/pubmed/7609181>
982. Hong, J.Y., *et al.* Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. *Anesthesiology*, 2010. 113: 672.
<https://www.ncbi.nlm.nih.gov/pubmed/20693884>
983. Jo, Y.Y., *et al.* Ketorolac or fentanyl continuous infusion for post-operative analgesia in children undergoing ureteroneocystostomy. *Acta Anaesthesiol Scand*, 2011. 55: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/21083540>
984. Miller, O.F., *et al.* Early hospital discharge for intravesical ureteroneocystostomy. *J Urol*, 2002. 167: 2556.
<https://www.ncbi.nlm.nih.gov/pubmed/11992088>
985. Park, J.M., *et al.* Ketorolac suppresses postoperative bladder spasms after pediatric ureteral reimplantation. *Anesth Analg*, 2000. 91: 11.
<https://www.ncbi.nlm.nih.gov/pubmed/10866879>
986. Routh, J.C., *et al.* Ketorolac is underutilized after ureteral reimplantation despite reduced hospital cost and reduced length of stay. *Urology*, 2010. 76: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/20138342>
987. Kumar, R., *et al.* Dorsal lumbotomy incision for pediatric pyeloplasty--a good alternative. *Pediatr Surg Int*, 1999. 15: 562.
<https://www.ncbi.nlm.nih.gov/pubmed/10631734>
988. Piedrahita, Y.K., *et al.* Is one-day hospitalization after open pyeloplasty possible and safe? *Urology*, 2006. 67: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/16413360>
989. Berta, E., *et al.* Single injection paravertebral block for renal surgery in children. *Paediatr Anaesth*, 2008. 18: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/18482238>
990. Lonnqvist, P.A., *et al.* Paravertebral vs epidural block in children. Effects on postoperative morphine requirement after renal surgery. *Acta Anaesthesiol Scand*, 1994. 38: 346.
<https://www.ncbi.nlm.nih.gov/pubmed/8067221>
991. Ben-Meir, D., *et al.* Continuous epidural versus nonepidural analgesia for post-pyeloplasty pain in children. *J Urol*, 2009. 182: 1841.
<https://www.ncbi.nlm.nih.gov/pubmed/19692062>
992. Dingemann, J., *et al.* Perioperative analgesia strategies in fast-track pediatric surgery of the kidney and renal pelvis: lessons learned. *World J Urol*, 2010. 28: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/19565247>
993. Freilich, D.A., *et al.* The effectiveness of aerosolized intraperitoneal bupivacaine in reducing postoperative pain in children undergoing robotic-assisted laparoscopic pyeloplasty. *J Pediatr Urol*, 2008. 4: 337.
<https://www.ncbi.nlm.nih.gov/pubmed/18790415>

5. CONFLICT OF INTEREST

All members of the Paediatric Urology Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Urological Trauma

N.D. Kitrey (Chair), N. Djakovic, M. Gonsalves, F.E. Kuehhas,
N. Lumen, E. Serafetinidis, D.M. Sharma
Guidelines Associates: Y. Abu-Ghanem, P-J. Elshout,
A. Sujenthiran, E. Veskimäe

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Guidelines Panel for Urological Trauma have prepared these guidelines in order to assist medical professionals in the management of urological trauma in adults. Paediatric trauma is addressed in the EAU Paediatric Urology Guidelines [1].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions – also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urological Trauma Guidelines Panel consists of an international group of experts, including urologists and an interventional radiologist, with particular expertise in urological trauma. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website Uroweb: <http://uroweb.org/guideline/urological-trauma/?type=panel>.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal, are also available [2-5]. All documents can be viewed through the EAU website: <http://uroweb.org/guideline/urological-trauma/>.

1.4 Publication history

The Urological Trauma Guidelines were first published in 2003. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. All sections of the 2017 Urological Trauma guidelines, with the exception of sections relating to imaging modalities, have been updated.

2. METHODS

2.1 Evidence sources

For the 2017 Urological Trauma Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Urological Trauma Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between January 2005 and May 31st 2016. A total of 14,498 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <http://uroweb.org/guideline/urological-trauma/?type=appendices-publications>. The majority of identified publications were comprised of case reports and retrospective case series. The lack of high-powered randomised controlled trials (RCTs) makes it difficult to draw meaningful conclusions. The panel recognises this critical limitation.

Specific sections were updated by way of systematic reviews based on topics or questions prioritised by the Guideline Panel. These reviews were performed using standard Cochrane systematic review methodology; <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>.

Systematic review results included in the 2017 Urological Trauma Guidelines include:

- Is conservative/minimally-invasive management of Grade 4-5 renal trauma safe and effective compared with open surgical exploration [6]?
- What are the comparative outcomes of early endoscopic re-alignment versus suprapubic diversion alone for pelvic fracture related urethral injuries [7]?

Recommendations in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8]. Additional methodology information can be found

in the general Methodology section of this print, and online at the EAU website: <http://uroweb.org/guidelines/>. A list of Associations endorsing the EAU Guidelines can also be viewed on line at the above address.

2.2 Peer review

The Urological trauma Guidelines were peer reviewed prior to publication in 2015.

3. EPIDEMIOLOGY & CLASSIFICATION

3.1 Definition and Epidemiology

Trauma is defined as a physical injury or a wound to living tissue caused by an extrinsic agent. Trauma is the sixth leading cause of death worldwide, accounting for 10% of all mortalities. It accounts for approximately five million deaths each year and causes disability to millions more [9, 10].

About half of all deaths due to trauma are in people aged 15-45 years with trauma being the leading cause of death in this age group [11]. Death from injury is twice as common in males, especially in relation to motor vehicle accidents (MVAs) and interpersonal violence. Trauma is therefore a serious public health problem with significant social and economic costs.

Significant variation exists in the causes and the effects of traumatic injuries between geographical areas, and between low, middle, and high-income countries. It should be noted that alcohol and drug abuse increase the rate of traumatic injuries by precipitating interpersonal violence, child and sexual abuse, and MVAs [12].

3.1.1 Genito-Urinary Trauma

Genito-urinary trauma is seen in both sexes and in all age groups, but is more common in males. The kidney is the most commonly injured organ in the genito-urinary system and renal trauma is seen in up to 5% of all trauma cases [13, 14], and in 10% of all abdominal trauma cases [15]. In MVAs, renal trauma is seen after direct impact into the seatbelt or steering wheel (frontal crashes) or from body panel intrusion in side-impact crashes [16].

Ureteral trauma is relatively rare and mainly due to iatrogenic injuries or penetrating gunshot wounds, both in military and civilian settings [17].

Traumatic bladder injuries are usually due to blunt causes (MVAs) and associated with pelvic fracture [18], although they may also be a result of iatrogenic trauma.

The anterior urethra is most commonly injured by blunt or "fall-astride" trauma, whereas the posterior urethra is usually injured in pelvic fracture cases, the majority of which are seen in MVAs [19].

Genital trauma is much more common in males due to anatomical considerations, more frequent participation in physical sports, violent events and war-fighting. Of all genito-urinary injuries, a third to two thirds involve the external genitalia [20].

3.2 Classification of trauma

Traumatic injuries are classified by the World Health Organization (WHO) into intentional (either interpersonal violence related, war-related or self-inflicted injuries), and unintentional injuries (mainly MVAs, falls, and other domestic accidents). Intentional trauma accounts for approximately half of the trauma-related deaths worldwide [10]. A specific type of unintentional injury is iatrogenic injury which is created during therapeutic- or diagnostic procedures by healthcare personnel.

Traumatic insults are classified according to the basic mechanism of the injury into penetrating, when an object pierces the skin, and blunt injuries.

Penetrating trauma is further classified according to the velocity of the projectile into:

1. high-velocity projectiles (e.g. rifle bullets - 800-1,000 m/sec);
2. medium-velocity projectiles (e.g. handgun bullets - 200-300 m/sec);
3. low-velocity items (e.g. knife stab).

High-velocity weapons inflict greater damage because the bullets transmit large amounts of energy to the tissues. They form a temporary expansive cavitation that immediately collapses and creates shear forces and destruction in a much larger area than the projectile tract itself. Cavity formation disrupts tissue, ruptures blood vessels and nerves, and may fracture bones away from the path of the missile. In lower velocity injuries, the damage is usually confined to the projectile tract.

Blast injury is a complex cause of trauma as it commonly includes both blunt and penetrating

trauma, and may also be accompanied by a burn injury.

Several classifications are used to describe the severity and the features of a traumatic injury. The most common is the AAST (American Association for the Surgery of Trauma) injury scoring scale, which is widely used in renal trauma (see Section 4.1.1.3) <http://www.aast.org/library/traumatools/injuryscoringscales.aspx> [21]. For the other urological organs, general practice is that injuries are described by their anatomical site and severity (partial/complete); therefore, the elaborated AAST tables are omitted from these guidelines.

3.2.1 **Initial evaluation and treatment**

The initial emergency assessment of a trauma patient is beyond the focus of these guidelines, and is usually carried out by emergency medicine and trauma specialised personnel. The first priority is stabilisation of the patient and treatment of associated life-threatening injuries. The initial treatment should include securing the airway, controlling external bleeding and resuscitation of shock. In many cases, physical examination is carried out during stabilisation of the patient.

A direct history is obtained from conscious patients, while witnesses and emergency personnel can provide valuable information about unconscious or seriously injured patients. In penetrating injuries, important information includes the size of the weapon in stabbings, and the type and calibre of the weapon used in gunshot wounds. The medical history should be as detailed as possible, as pre-existing organ dysfunction can have a negative effect on trauma patient outcome [22, 23]. It is essential that all persons treating trauma patients are aware of the risk of hepatitis B and C infection. An infection rate of 38% was reported among males with penetrating wounds to the external genitalia [24]. In any penetrating trauma, tetanus vaccination should be considered according to the patient's vaccination history and the features of the wound itself (Centres for Disease Control and Prevention [CDC] tetanus wound management) [25].

4. UROGENITAL TRAUMA GUIDELINES

4.1 **Renal Trauma**

4.1.1 **Epidemiology, aetiology and pathophysiology**

4.1.1.1 *Definition and impact of the disease*

Renal trauma occurs in approximately 1-5% of all trauma cases [14, 26]. Renal injuries are associated with young age and male gender, the incidence is approximately 4.9 per 100,000 of the population [27]. Most injuries can be managed conservatively as advances in imaging and treatment strategies have decreased the need for surgical intervention and increased organ preservation [15, 28, 29].

4.1.1.2 *Mode of injury*

4.1.1.2.1 *Blunt renal injuries*

Blunt mechanisms include MVAs, falls, vehicle-associated pedestrian accidents and assault [30]. A direct blow to the flank or abdomen during sports activities is another cause. Sudden deceleration or a crush injury may result in contusion or laceration of the parenchyma or the renal hilum. In general, renal vascular injuries occur in less than 5% of blunt abdominal trauma, while isolated renal artery injury is very rare (0.05-0.08%) [15] and renal artery occlusion is associated with rapid deceleration injuries.

4.1.1.2.2 *Penetrating renal injuries*

Gunshot and stab wounds represent the most common causes of penetrating injuries and tend to be more severe and less predictable than blunt trauma. In urban settings, the percentage of penetrating injuries can be 20% or higher [31, 32]. Bullets have the potential for greater parenchymal destruction and are most often associated with multiple-organ injuries [33]. Penetrating injury produces direct tissue disruption of the parenchyma, vascular pedicles, or collecting system.

4.1.1.3 *Classification systems*

The most commonly used classification system is that of the AAST [21] (Table 4.1.1). This validated system has clinical relevance and helps to predict the need for intervention [16, 34, 35]. It also predicts morbidity after blunt or penetrating injury and mortality after blunt injury [16].

Table 4.1.1: AAST renal injury grading scale

Grade*	Description of injury
1	Contusion or non-expanding subcapsular haematoma No laceration
2	Non-expanding peri-renal haematoma Cortical laceration < 1 cm deep without extravasation
3	Cortical laceration > 1 cm without urinary extravasation
4	Laceration: through corticomedullary junction into collecting system <i>or</i> Vascular: segmental renal artery or vein injury with contained haematoma, or partial vessel laceration, or vessel thrombosis
5	Laceration: shattered kidney <i>or</i> Vascular: renal pedicle or avulsion

*Advance one grade for bilateral injuries up to grade III.

Proposals for changes to the AAST classification include a sub-stratification of the intermediate grade injury into grade 4a (low-risk cases likely to be managed non-operatively) and grade 4b (high-risk cases likely to benefit from angiographic embolisation, repair or nephrectomy), based on the presence of radiographic risk factors, including peri-renal haematoma, intravascular contrast extravasation and laceration complexity [36], as well as a suggestion that grade 4 injuries comprise all collecting system injuries, including ureteropelvic junction (UPJ) injuries of any severity and segmental arterial and venous injuries, while grade 5 injuries should include only hilar injuries, including thrombotic events [37].

4.1.2 **Diagnostic evaluation**

4.1.2.1 *Patient history and physical examination*

Vital signs should be recorded throughout the diagnostic evaluation. Possible indicators of major injury include a history of a rapid deceleration event (fall, high-speed MVAs) or a direct blow to the flank. In the early resuscitation phase, special consideration should be given to pre-existing renal disease [38]. In patients with a solitary kidney, the entire functioning renal unit may be endangered [39, 40]. Since pre-existing abnormality makes injury more likely following trauma, hydronephrosis due to UPJ abnormality, calculi, cysts and tumours may complicate a minor injury [40].

Physical examination may reveal an obvious penetrating trauma from a stab wound to the lower thoracic back, flanks and upper abdomen, or bullet entry or exit wounds. In stab wounds, the extent of the entrance wound may not accurately reflect the depth of penetration.

Blunt trauma to the back, flank, lower thorax or upper abdomen may result in renal injury. Flank pain, ecchymoses, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness, raise the suspicion of renal involvement.

4.1.2.1.1 Recommendations for patient history and physical examination

Recommendations	LE	GR
Assess haemodynamic stability upon admission.	3	A*
Obtain a history from conscious patients, witnesses and rescue team personnel with regard to the time and setting of the incident.	4	A*
Record past renal surgery, and known pre-existing renal abnormalities (ureteropelvic junction obstruction, large cysts, lithiasis).	4	A*

*Upgraded based on panel consensus.

4.1.2.2 *Laboratory evaluation*

Urinalysis, haematocrit and baseline creatinine are the most important tests. Haematuria, either non-visible or visible is often seen, but is neither sensitive nor specific enough to differentiate between minor and major injuries [41].

Major injury, such as disruption of the UPJ, pedicle injuries, segmental arterial thrombosis and approximately 9% of patients with stab wounds and renal injury may occur without haematuria [42, 43]. Haematuria that is out of proportion to the history of trauma may suggest pre-existing pathology [44]. A urine dipstick is an acceptable, reliable and rapid test to evaluate haematuria, however, the rate of false-negative

results ranges from 3-10% [45].

Serial haematocrit determination is part of the continuous evaluation. A decrease in haematocrit and the requirement for blood transfusions are indirect signs of the rate of blood loss, and along with the patient's response to resuscitation, are valuable in the decision-making process. However, until evaluation is complete, it will not be clear whether this is due to renal trauma and/or associated injuries. Baseline creatinine measurement reflects renal function prior to the injury. An increased creatinine level usually reflects pre-existing renal pathology.

4.1.2.2.1 Recommendations for laboratory evaluation

Recommendations	LE	GR
Test for haematuria in a patient with suspected renal injury.	3	A*
Measure creatinine level to identify patients with impaired renal function prior to injury.	3	C

**Upgraded based on panel consensus.*

4.1.2.3 Imaging: criteria for radiographic assessment

Decisions to image in suspected renal trauma are based on the mechanism of injury and clinical findings. The goals of imaging are to grade the renal injury, document pre-existing renal pathology, demonstrate presence of the contralateral kidney and identify injuries to other organs. Haemodynamic status will determine the initial imaging pathway with unstable patients potentially requiring immediate damage control laparotomy.

There is general agreement in the literature that renal imaging should be undertaken in blunt trauma if there is visible haematuria or non-visible haematuria and hypotension (systolic blood pressure < 90 mmHg) [30, 46-49]. Patients with non-visible haematuria and no shock after blunt trauma have a low likelihood of concealing significant injury. Other accepted indications for renal imaging in blunt trauma are rapid deceleration injury, direct flank trauma, flank contusions, fracture of the lower ribs and fracture of the thoracolumbar spine, regardless of the presence or absence of haematuria [30, 46-49].

In patients with penetrating trauma, with the suspicion of renal injury, imaging is indicated regardless of haematuria [30, 46-49].

4.1.2.3.1 Ultrasonography (US)

In the setting of abdominal trauma, US is used widely to assess for the presence of haemoperitoneum. However, grey-scale US is insensitive to solid abdominal organ injury [50-52] and the American College of Radiologists (ACR) Renal Trauma guidelines considers US usually not appropriate in renal trauma [47].

The use of contrast enhanced US (CEUS) with microbubbles increases the sensitivity of US to solid organ injury [53]. Its usefulness in renal injury is limited because microbubbles are not excreted into the collecting system, therefore CEUS cannot reliably demonstrate injuries to the renal pelvis or ureter. It is not widely used, although it is a possible no-radiation alternative to computed tomography (CT) in the follow-up of renal trauma [54-56].

4.1.2.3.2 Computed tomography

Computed tomography is the imaging modality of choice in haemodynamically stable patients following blunt or penetrating trauma. Computed tomography is widely available, can quickly and accurately identify and grade renal injury [57], establish the presence of the contralateral kidney and demonstrate concurrent injuries to other organs. Integration of whole body CT into the initial management of polytrauma patients significantly increases the probability of survival [58]. Although the AAST system of grading renal injuries is primarily based on surgical findings, there is a good correlation with CT appearances [58, 59].

In the setting of isolated renal trauma, multiphase CT allows the most comprehensive assessment of the injured kidney and includes pre-contrast and post-contrast arterial, nephrographic and delayed (pyelographic) phase images. Pre-contrast images may help identify subcapsular haematomas obscured on post-contrast sequences [59]. Administration of intravenous iodinated contrast media is essential. Concerns regarding contrast media worsening outcomes via renal parenchymal toxicity are likely unwarranted, with low rates of contrast-induced nephropathy seen in trauma patients [60]. Arterial phase images allow assessment of vascular injury and presence of active extravasation of contrast. Nephrographic phase images optimally demonstrate parenchymal contusions and lacerations. Delayed phase imaging reliably identifies collecting system/ureteric injury [61]. In practice, trauma patients usually undergo standardised whole body imaging protocols and multiphase imaging of the renal tract will not be routinely performed. If there is suspicion that renal injuries have not been fully evaluated, repeat renal imaging should be considered.

4.1.2.3.3 Other imaging modalities

Intravenous pyelography (IVP)

Intravenous pyelography has been superseded by cross-sectional imaging and should only be performed when CT is not available. Intravenous pyelography can be used to confirm function of the injured kidney and presence of the contralateral kidney [47].

Intraoperative pyelography

One-shot, intraoperative IVP remains a useful technique to confirm the presence of a functioning contralateral kidney in patients too unstable to undergo pre-operative imaging [62]. The technique consists of a bolus intravenous injection of 2 mL/kg of radiographic contrast followed by a single plain film taken after ten minutes.

Magnetic resonance imaging (MRI)

The diagnostic accuracy of MRI in renal trauma is similar to that of CT [63, 64]. However, the logistical challenges of moving a trauma patient to the MRI suite and the need for MRI-safe equipment make routine evaluation of trauma patients by this imaging modality impractical.

Radionuclide scans

Radionuclide scans do not play a role in the immediate evaluation of renal trauma patients.

4.1.3 **Disease management**

4.1.3.1 *Conservative management*

4.1.3.1.1 Blunt renal injuries

Haemodynamic stability is the primary criterion for the management of all renal injuries. Non-operative management has become the treatment of choice for most renal injuries. In stable patients, this means supportive care with bed-rest and observation. Primary conservative management is associated with a lower rate of nephrectomies, without any increase in the immediate or long-term morbidity [65]. Hospitalisation or prolonged observation for evaluation of possible injury after a normal abdominal CT scan, when combined with clinical judgment, is unnecessary in most cases [66]. All grade 1 and 2 injuries, either due to blunt or penetrating trauma, can be managed non-operatively. For the treatment of grade 3 injuries, most studies support expectant treatment [67-69].

Most patients with grade 4 and 5 injuries present with major associated injuries, and consequently often undergo exploration and nephrectomy [70], although emerging data indicate that many of these patients can be managed safely with an expectant approach [71]. An initially conservative approach is feasible in stable patients with devitalised fragments [72], although these injuries are associated with an increased rate of complications and late surgery [73]. Patients diagnosed with urinary extravasation from solitary injuries can be managed without major intervention with a resolution rate of > 90% [71, 74]. Similarly, unilateral main arterial injuries are normally managed non-operatively in a haemodynamically stable patient with surgical repair reserved for bilateral artery injuries or injuries involving a solitary functional kidney. Conservative management is also advised in the treatment of unilateral complete blunt arterial thrombosis. However, a blunt arterial thrombosis in multiple trauma patients is usually associated with severe injuries and attempts at repair are usually unsuccessful [75].

4.1.3.1.2 Penetrating renal injuries

Penetrating wounds have traditionally been approached surgically. A systematic approach based on clinical, laboratory and radiological evaluation minimises the incidence of negative exploration without increasing morbidity from a missed injury [76]. Selective non-operative management of abdominal stab wounds is generally accepted following complete staging in stable patients [69, 77]. If the site of penetration by the stab wound is posterior to the anterior axillary line, 88% of such injuries can be managed non-operatively [78]. Stab wounds producing major renal injuries (grade 3 or higher) are more unpredictable and are associated with a higher rate of delayed complications if treated expectantly [79].

Isolated grade 4 injuries represent a unique situation where treatment of the patient is based solely on the extent of the renal injury. Gunshot injuries should be explored only if they involve the hilum or are accompanied by signs of ongoing bleeding, ureteral injuries, or renal pelvis lacerations [80]. Minor low-velocity gunshot and stab wounds may be managed conservatively with an acceptably good outcome [81]. In contrast, tissue damage due to high-velocity gunshot injuries can be more extensive and nephrectomy may be required. Non-operative management of penetrating injuries in selected stable patients is associated with a successful outcome in approximately 50% of stab wounds and up to 40% of gunshot wounds [82-84].

4.1.3.1.3 Interventional radiology

Angioembolisation has a central role in the non-operative management of blunt renal trauma in haemodynamically stable patients [85-87]. Currently there are no validated criteria to identify patients who require angioembolisation and its use in renal trauma remains heterogeneous. Generally, accepted CT findings indicating angioembolisation are active extravasation of contrast, arteriovenous fistula and pseudoaneurysm [88]. The presence of both active extravasation of contrast and a large haematoma (> 25 mm depth) predict the need for angioembolisation with good accuracy [88, 89]. Angioembolisation has been utilised in the non-operative management of all grades of renal injury, however it is likely to be most beneficial in the setting of high grade renal trauma (AAST > 3) [85-87]. Non-operative management of high-grade renal trauma, where angioembolisation is included in the management algorithm, can be successful in up to 94.9% of grade 3, 89% of grade 4 and 52% of grade 5 injuries [85, 86]. Increasing grade of renal injury is associated with increased risk of failed angioembolisation and need for repeat intervention [90]. Repeat embolisation prevents nephrectomy in 67% of patients and open surgery after failed embolisation usually results in nephrectomy [90, 91]. Despite concerns regarding parenchymal infarction and the use of iodinated contrast media, there is evidence to suggest angioembolisation does not affect the occurrence or course of acute kidney injury following renal trauma [92]. In severe polytrauma or high operative risk, the main artery may be embolised, either as a definitive treatment or to be followed by interval nephrectomy.

Available evidence regarding angioembolisation in penetrating renal trauma is sparse. One older study found angioembolisation is three times more likely to fail in penetrating trauma [76]. However, angioembolisation has been used successfully to treat arteriovenous fistulae and pseudoaneurysms in the non-operative management of penetrating renal trauma [93]. With studies reporting successful non-operative management of penetrating renal trauma, angioembolisation must be critically considered in this setting [93, 94].

4.1.3.2 Surgical management

4.1.3.2.1 Indications for renal exploration

The need for renal exploration can be predicted by considering the type of injury, transfusion requirements, blood urea nitrogen (BUN), creatinine and injury grade [95]. However, management of renal injury may also be influenced by the decision to explore or observe associated abdominal injuries [96]. Continuing haemodynamic instability and unresponsiveness to aggressive resuscitation due to renal haemorrhage is an indication for exploration, irrespective of the mode of injury [76, 97]. Other indications include an expanding or pulsatile peri-renal haematoma, identified at exploratory laparotomy, performed for associated injuries. Persistent extravasation or urinoma are usually managed successfully with endo-urological techniques. Inconclusive imaging and a pre-existing abnormality or an incidentally diagnosed tumour may require surgery even after minor renal injury [44].

Grade 5 vascular injuries are regarded as an absolute indication for exploration, but parenchymal grade 5 patients who are stable at presentation may be safely treated conservatively [98-101]. In these patients, intervention is predicted by the need for continued fluid and blood resuscitation, peri-renal haematoma size > 3.5 cm and the presence of intravascular contrast extravasation [36].

4.1.3.2.2 Operative findings and reconstruction

The overall exploration rate for blunt trauma is less than 10% [97], and may be even lower, as the conservative approach is increasingly adopted [102]. The goals of exploration following renal trauma are control of haemorrhage and renal salvage.

Most series suggest the transperitoneal approach for surgery [103, 104]. Access to the pedicle is obtained either through the posterior parietal peritoneum, which is incised over the aorta, just medial to the inferior mesenteric vein or by bluntly dissecting along the plane of the psoas muscle fascia, adjacent to the great vessels, and directly placing a vascular clamp on the hilum [105]. Stable haematomas detected during exploration for associated injuries should not be opened. Central or expanding haematomas indicate injuries of the renal pedicle, aorta, or vena cava and are potentially life-threatening [106].

In cases with unilateral arterial intimal disruption, repair can be delayed, especially in the presence of a normal contralateral kidney. However, prolonged warm ischaemia usually results in irreparable damage and renal loss. Entering the retroperitoneum and leaving the confined haematoma undisturbed within the perinephric fascia is recommended unless it is violated and cortical bleeding is noted; temporarily packing the fossa tightly with laparotomy pads can salvage the kidney [107]. Haemorrhage can occur while the patient is resuscitated, warmed, and awaits re-exploration, however, careful monitoring is sufficient. A brief period of controlled local urinary extravasation is unlikely to result in a significant adverse event or impact overall recovery. During the following 48 to 72 hours, CT scans can identify injuries and select patients for reconstruction or continued expectant management [108]. Ureteral stenting or nephrostomy diversion should be considered after delayed reconstruction due to the increased risk of post-operative urinary extravasation.

Feasibility of renal reconstruction should be judged during the operation. The overall rate of patients who undergo a nephrectomy during exploration is approximately 13%, usually in patients with penetrating injuries and higher rates of transfusion requirements, haemodynamic instability, and higher injury severity scores [109]. Other intra-abdominal injuries also slightly increase the need for nephrectomy [110]. Mortality is associated with overall severity of the injury and not often a consequence of the renal injury itself [111]. In gunshot injuries caused by a high-velocity bullet, reconstruction can be difficult and nephrectomy is often required [112]. Renorrhaphy is the most common reconstructive technique. Partial nephrectomy is required when non-viable tissue is detected. Watertight closure of the collecting system, if open, is desirable, although closing the parenchyma over the injured collecting system also has good results. If the capsule is not preserved, an omental pedicle flap or peri-renal fat bolster may be used for coverage [113]. The use of haemostatic agents and sealants in reconstruction can be helpful [114]. In all cases, drainage of the ipsilateral retroperitoneum is recommended. Following blunt trauma, repair of vascular injuries (grade 5) is seldom, if ever, effective [115]. Repair should be attempted in patients with a solitary kidney or bilateral injuries [116], but not in the presence of a functioning contralateral kidney [29]. Nephrectomy for main artery injury has outcomes similar to those of vascular repair and does not worsen post-treatment renal function in the short-term.

4.1.3.2.3 Recommendations for management of renal trauma

Recommendations	LE	GR
Manage stable patients with blunt renal trauma conservatively with close monitoring of vital signs.	3	B
Manage isolated grade 1-3 stab and low-velocity gunshot wounds in stable patients, expectantly.	3	B
Treat patients with active bleeding from renal injury, but without other indications for immediate abdominal operation, with angioembolisation.	3	B
Proceed with renal exploration in the presence of persistent haemodynamic instability, expanding or pulsatile peri-renal haematoma, grade 5 vascular injury or in case of exploration for associated injuries.	3	B
Attempt renal reconstruction if haemorrhage is controlled and there is sufficient viable renal parenchyma.	3	B

4.1.4 Follow-up

The risk of complications in patients who have been treated conservatively increases with injury grade. Repeat imaging two to four days after trauma minimises the risk of missed complications, especially in grade 3-5 blunt injuries [117]. The usefulness of frequent CT scanning after injury has never been satisfactorily proven. Computed tomography scans should always be performed on patients with fever, unexplained decreased haematocrit or significant flank pain. Repeat imaging can be safely omitted for patients with grade 1-4 injuries as long as they remain clinically well [118].

Nuclear scans are useful for documenting and tracking functional recovery following renal reconstruction [119]. Follow-up should involve physical examination, urinalysis, individualised radiological investigation, serial blood pressure measurement and serum determination of renal function [72]. A decline in renal function correlates directly with injury grade; this is independent of the mechanism of injury and the method of management [120, 121]. Follow-up examinations should continue until healing is documented and laboratory findings have stabilised, although checking for latent renovascular hypertension may need to continue for years [122]. In general, the literature is highly limited on the long-term consequences of renal tissue trauma.

4.1.4.1 Complications

Early complications, occurring less than one month after injury, include bleeding, infection, perinephric abscess, sepsis, urinary fistula, hypertension, urinary extravasation and urinoma. Delayed complications include bleeding, hydronephrosis, calculus formation, chronic pyelonephritis, hypertension, arteriovenous fistula, hydronephrosis and pseudo-aneurysms. Delayed retroperitoneal bleeding may be life-threatening and selective angiographic embolisation is the preferred treatment [123]. Perinephric abscess formation is best managed by percutaneous drainage, although open drainage may sometimes be required. Percutaneous management of complications may pose less risk of renal loss than re-operation, when infected tissues make reconstruction difficult [97].

Renal trauma is a rare cause of hypertension, and is mostly observed in young men. The frequency of post-traumatic hypertension is estimated to be less than 5% [124, 125]. Hypertension may occur acutely as a result of external compression from peri-renal haematoma (Page kidney), or chronically due to compressive

scar formation. Renin-mediated hypertension may occur as a long-term complication, aetiologies include renal artery thrombosis, segmental arterial thrombosis, renal artery stenosis (Goldblatt kidney), devitalised fragments and arteriovenous fistulae (AVF). Arteriography is informative in cases of post-traumatic hypertension. Treatment is required if the hypertension persists and could include medical management, excision of the ischaemic parenchymal segment, vascular reconstruction, or total nephrectomy [126].

Urinary extravasation after reconstruction often subsides without intervention as long as ureteral obstruction and infection are not present. Ureteral retrograde stenting may improve drainage and allow healing [127]. Persistent urinary extravasation from an otherwise viable kidney after blunt trauma often responds to stent placement and/or percutaneous drainage [128].

Arteriovenous fistulae usually present with delayed onset of significant haematuria, most often after penetrating trauma. Percutaneous embolisation is often effective for symptomatic AVF, but larger ones may require surgery [129]. Post-procedural complications include infection, sepsis, urinary fistula, and renal infarction [130]. The development of pseudo-aneurysm is a rare complication following blunt trauma. In numerous case reports, transcatheter embolisation appears to be a reliable minimally invasive solution [131]. Acute renal colic from a retained missile has been reported, and should be managed endoscopically, if possible [132].

4.1.4.2 Recommendations for follow-up

Recommendations	LE	GR
Repeat imaging in case of fever, worsening flank pain, or falling haematocrit.	3	B
Follow-up approximately three months after major renal injury with physical examination, urinalysis, individualised radiological investigation, including nuclear scintigraphy, serial blood pressure measurements and renal function tests.	3	C

4.1.5 Iatrogenic renal injuries

4.1.5.1 Introduction

Iatrogenic renal trauma is rare, but can lead to significant morbidity.

4.1.5.2 Incidence and aetiology

The commonest causes of iatrogenic renal injuries are listed in Table 4.1.2 [133].

Table 4.1.2: Incidence and aetiology of commonest iatrogenic renal trauma during various procedures

Procedure	Haemorrhage	AVF	Pseudo-aneurysm	Renal pelvis Injury	Aortocaliceal fistula	Foreign body
Nephrostomy	+		+	+		
Biopsy	+ (0.5-1.5%)	+	+ (0.9%)			
PCNL	+	+		+		
Laparoscopic surgery (oncology)	+					
Open surgery (oncology)	+		+ (0.43%)			+
Transplantation	+	+	+		+	
Endopyelotomy	+			+		+
Endovascular procedure	+ (1.6%)					

AVF = arteriovenous fistulae; PCNL = percutaneous nephrolithotomy.

Large haematomas after biopsy (0.5-1.5%) are caused by laceration or arterial damage [134]. Renal artery and intraparenchymal pseudo-aneurysms (0.9%) may be caused by percutaneous biopsy, nephrostomy, and partial nephrectomy (0.43%) [135]. In percutaneous nephrolithotomy (PCNL), haemorrhage is the most dangerous iatrogenic renal trauma, especially when punctures are too medial or directly entering the renal pelvis. Other injuries include AVF or a tear in the pelvicaliceal system.

Iatrogenic renal injuries associated with renal transplantation include AVF, intrarenal pseudo-aneurysms, arterial dissection and arterio-caliceal fistulas. Pseudo-aneurysm is a rare complication of allograft biopsy. Although the overall complication rate following biopsy in transplanted kidneys is 9% (including haematoma, AVF, visible haematuria and infection), vascular complications requiring intervention account for

0.2-2.0% [136]. Predisposing factors include hypertension, renal medullary disease, central biopsies, and numerous needle passes [137]. Arteriovenous fistulae and pseudo-aneurysms can occur in 1-18% of allograft biopsies [134].

Extra-renal pseudo-aneurysms after transplantation procedures generally occur at the anastomosis, in association with local or haematogenous infection. Arterial dissection related to transplantation is rare and presents in the early post-operative period [138].

Iatrogenic renal trauma associated with endopyelotomy is classified as major (vascular injury), and minor (urinoma) [139]. Patients undergoing cryoablation for small masses via the percutaneous or the laparoscopic approach may have asymptomatic perinephric haematoma and self-limiting urine leakage.

Vascular injury is a rare complication (1.6%) of endovascular interventions in contrast to patients with surgical injuries. The renal vessels are vulnerable mainly during oncological procedures [140]. Renal foreign bodies, with retained sponges or wires during open or endo-urological procedures, are uncommon.

4.1.5.3 *Diagnosis*

Haematuria is common after insertion of nephrostomies, but massive retroperitoneal haemorrhage is rare. Following percutaneous biopsy, AVF may occur with severe hypertension. A pseudo-aneurysm should be suspected if the patient presents with flank pain and decreasing haematocrit, even in the absence of haematuria.

During PCNL, acute bleeding may be caused by injury to the anterior or posterior segmental arteries, whilst late post-operative bleeding may be caused by interlobar and lower-pole arterial lesions, AVF and post-traumatic aneurysms [141]. Duplex US and CT angiography can be used to diagnose vascular injuries. A close watch on irrigation fluid input and output is required to ensure early recognition of fluid extravasation. Intra-operative evaluation of serum electrolytes, acid-base status, oxygenation, and monitoring of airway pressure are good indicators of this complication.

In arterial dissection related to transplantation, symptoms include anuria and a prolonged dependence on dialysis. Doppler US can demonstrate compromised arterial flow. Dissection can lead to thrombosis of the renal artery and/or vein.

After angioplasty and stent-graft placement in the renal artery, during which wire or catheters may enter the parenchyma and penetrate through the capsule, possible radiological findings include AVF, pseudo-aneurysm, arterial dissection and contrast extravasation. Common symptoms of pseudo-aneurysms are flank pain and visible haematuria within two or three weeks after surgery [142]. Transplant AVF and pseudo-aneurysms may be asymptomatic or may cause visible haematuria or hypovolemia due to shunting and the 'steal' phenomenon, renal insufficiency, hypertension, and high output cardiac failure.

Patients with extrarenal pseudo-aneurysms (post-transplantation) may present with infection/bleeding, swelling, pain and intermittent claudication. Doppler US findings for AVFs include high-velocity, low-resistance, spectral waveforms, with focal areas of disorganised colour flow outside the normal vascular borders, and possibly a dilated vein [143]. Pseudo-aneurysms appear on US as anechoic cysts, with intracystic flow on colour Doppler US.

Potential complications of retained sponges include abscess formation, fistula formation to the skin or intestinal tract, and sepsis. Retained sponges may look like pseudo-tumours or appear as solid masses. Magnetic resonance imaging clearly shows the characteristic features [144]. Absorbable haemostatic agents may also produce a foreign body giant cell reaction, but the imaging characteristics are not specific. Retained stents, wires, or fractured Acucise cutting wires may also present as foreign bodies and can serve as a nidus for stone formation [145].

4.1.5.4 *Management*

If a nephrostomy catheter appears to transfix the renal pelvis, significant arterial injury is possible. The misplaced catheter should be withdrawn and embolisation may rapidly arrest the haemorrhage. Computed tomography can also successfully guide repositioning of the catheter into the collecting system [146]. Small subcapsular haematomas after insertion of nephrostomies resolve spontaneously, whilst AVFs are best managed by embolisation. AVF and pseudo-aneurysms after biopsy are also managed by embolisation [147].

During PCNL, bleeding can be venous or arterial. In major venous trauma with haemorrhage, patients with concomitant renal insufficiency can be treated without open exploration or angiographic embolisation using a Council-tip balloon catheter [148]. In the case of profuse bleeding at the end of a PCNL, conservative management is usually effective. The patient should be placed in the supine position, clamping the nephrostomy catheter and forcing diuresis. Super-selective embolisation is required in less than 1% of cases and has proved effective in more than 90% [149]. Short-term deleterious effects are more pronounced in patients with a solitary kidney, but long-term follow-up shows functional and morphological improvements [150]. Termination of PCNL if the renal pelvis is torn or ruptured is a safe choice. Management requires close monitoring, placement of an abdominal or retroperitoneal drain and supportive measures [151]. Most surgical

venous injuries include partial lacerations that can be managed with various techniques, such as venorrhaphy, patch angioplasty with autologous vein, or an expanded polytetrafluoroethylene (ePTFE) graft [152]. If conservative measures fail in cases of pseudo-aneurysm and clinical symptoms or a relevant decrease in haemoglobin occurs, transarterial embolisation should be considered [153]. As the success rate is similar for initial and repeat interventions, a repeat intervention is justified when the clinical course allows this [90].

Traditionally, patients with post-operative haemorrhage following intra-abdominal laparoscopic surgery of the kidney require laparotomy. Pseudo-aneurysms and AVF are uncommon after minimally invasive partial nephrectomy, but can lead to significant morbidity. Temporary haemostasis occurs with coagulation and/or tamponade, but later degradation of the clot, connection with the extravascular space, and possible fistula formation within the collecting system may develop. Patients typically present with visible haematuria, even though they may also experience flank pain, dizziness and fever. Embolisation is the reference standard for both diagnosis and treatment in the acute setting, although CT can be used if the symptoms are not severe and/or the diagnosis is ambiguous. Reports have described good preservation of renal function after embolisation [154].

Endoluminal management after renal transplantation consists of stabilising the intimal flap with stent placement. Embolisation is the treatment of choice for a symptomatic transplant AVF or enlarging pseudo-aneurysm [155]. Super-selective embolisation with a coaxial catheter and metallic coils helps to limit the loss of normal functioning graft tissue [156]. Failure of embolisation is associated with a high nephrectomy rate. The long-term outcome depends on the course of the transplant and the amount of contrast medium used during the procedure.

Surgical treatment for AVF consists of partial or total nephrectomy or arterial ligation, which results in loss of part of the transplant or the entire transplant. To date, surgery has been the main approach in the treatment of renal vascular injuries. In patients with retroperitoneal haematoma, AVF, and haemorrhagic shock, interventional therapy is associated with a lower level of risk compared to surgery [157]. Renal arteriography followed by selective embolisation can confirm the injury. In injuries during angioplasty and stent-graft placement, transcatheter embolisation is the first choice of treatment [158]. The treatment for acute iatrogenic rupture of the main renal artery is balloon tamponade. If this fails, immediate availability of a stent graft is vital [159]. The true nature of lesions caused by foreign bodies is revealed after exploration.

4.1.5.5 Summary of evidence and recommendations for the management of iatrogenic renal injuries

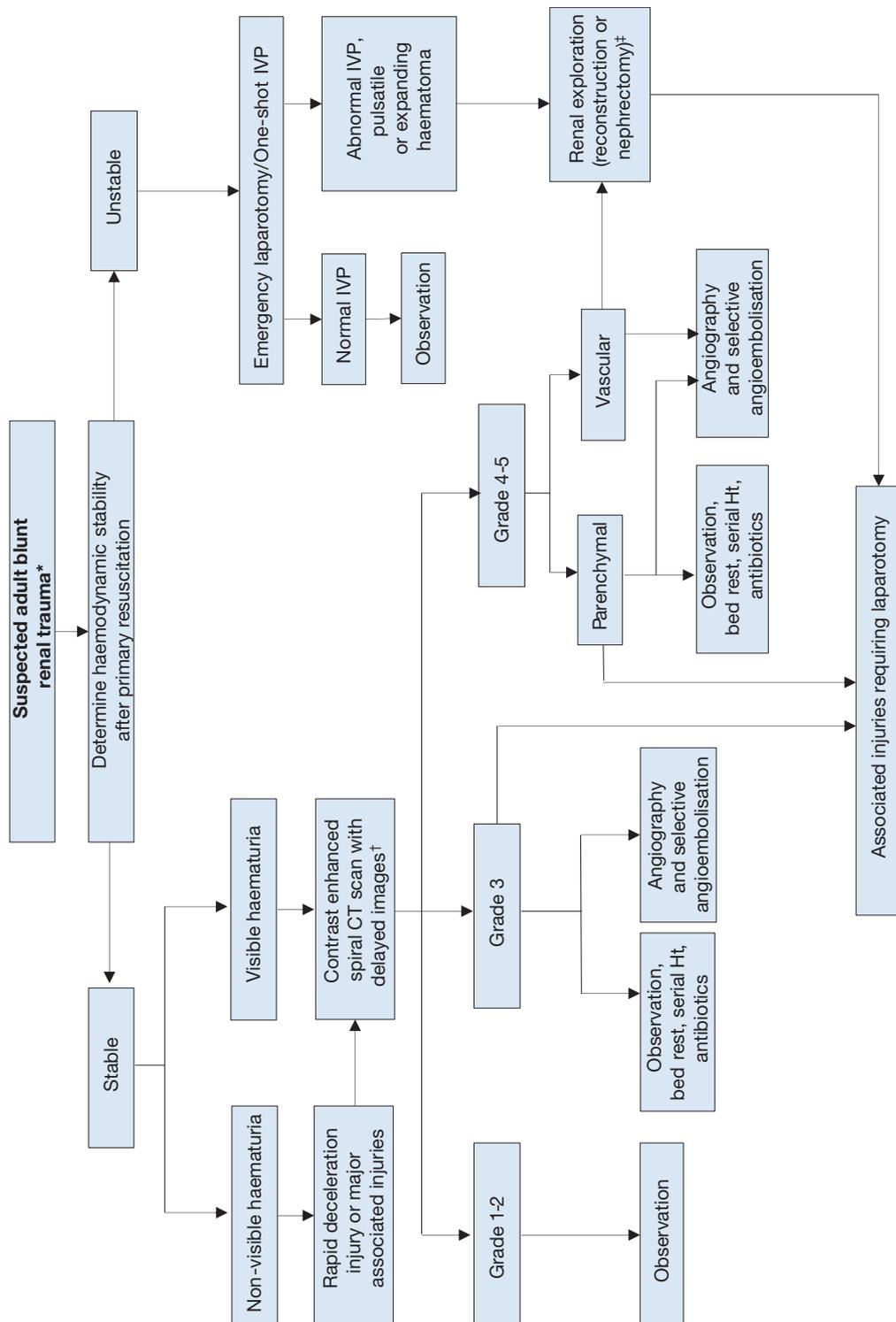
Summary of evidence	LE
Iatrogenic renal injuries are procedure-dependent (1.8-15%).	3
Significant injury requiring intervention is rare.	3
The most common injuries are vascular.	3
Renal allografts are more susceptible.	3
Injuries occurring during surgery are rectified immediately.	3
Symptoms suggestive of a significant injury require investigation.	3

Recommendations	LE	GR
Repeat imaging in case of fever, worsening flank pain, or falling haematocrit.	3	B
Follow-up approximately three months after major renal injury with physical examination, urinalysis, individualised radiological investigation, including nuclear scintigraphy, serial blood pressure measurements and renal function tests.	3	C

4.1.6 Algorithms

Figures 4.1.1 and 4.1.2 show the suggested treatment for blunt and penetrating renal injuries in adults.

Figure 4.1.1 Evaluation of blunt renal trauma in adults



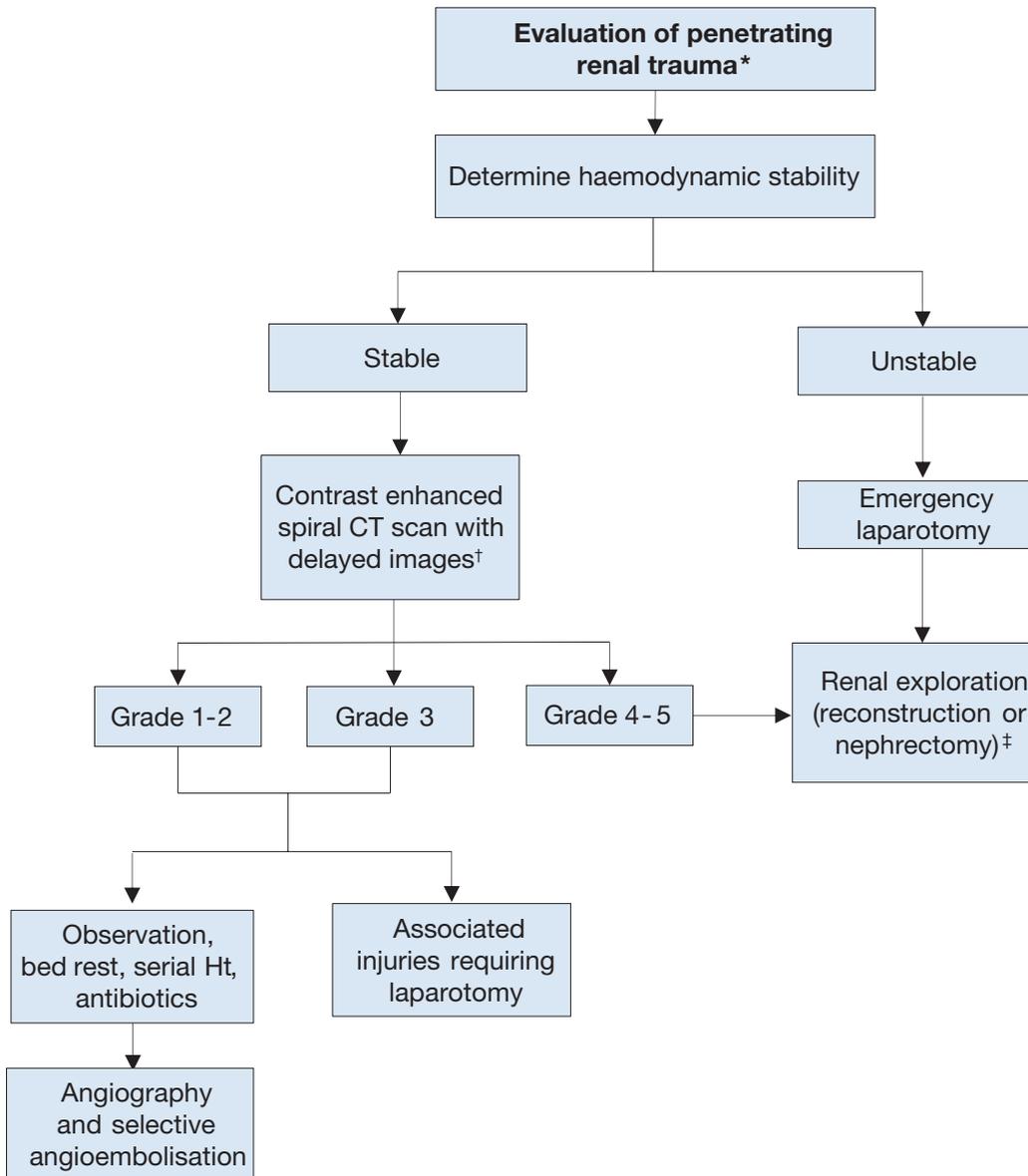
* Suspected renal trauma results from reported mechanism of injury and physical examination.

† Renal imaging: CT scans are the gold standard for evaluating blunt and penetrating renal injuries in stable patients. In settings where CT is not available, the urologist should rely on other imaging modalities (IVP, angiography, radiographic scintigraphy, MRI).

‡ Renal exploration: Although renal salvage is a primary goal for the urologist, decisions concerning the viability of the organ and the type of reconstruction are made during the operation.

CT = computed tomography; Ht = haematocrit; IVP = intravenous pyelography.

Figure 4.1.2 Evaluation of penetrating renal trauma in adults



Suspected renal trauma results from reported mechanism of injury and physical examination.

† Renal imaging: CT scans are the gold standard for evaluating blunt and penetrating renal injuries in stable patients. In settings where CT is not available, the urologist should rely on other imaging modalities (IVP, angiography, radiographic scintigraphy, MRI).

‡ Renal exploration: Although renal salvage is a primary goal for the urologist, decisions concerning the viability of the organ and the type of reconstruction are made during the operation.

CT = computed tomography; Ht = haematocrit.

4.2 Ureteral Trauma

4.2.1 Incidence

Trauma to the ureters is relatively rare as they are protected from injury by their small size, mobility, and the adjacent vertebrae, bony pelvis and muscles. Iatrogenic trauma is the commonest cause of ureteral injury (approximately 80%) [160]. It is seen in open, laparoscopic or endoscopic surgery and is often missed intra-operatively. Any trauma to the ureter may result in severe sequelae.

4.2.2 Epidemiology, aetiology, and pathophysiology

Overall, ureteral trauma accounts for 1-2.5% of urinary tract trauma [17, 160-162], with even higher rates in modern combat injuries [163]. Penetrating external ureteral trauma, mainly caused by gunshot wounds, dominates most of the modern series, both civilian and military [17, 160, 164]. About one-third of cases of external trauma to the ureters are caused by blunt trauma, mostly road traffic injuries [161, 162].

Ureteral injury should be suspected in all cases of penetrating abdominal injury, especially gunshot wounds, as it occurs in 2-3% of cases [160]. It should also be suspected in blunt trauma with a deceleration mechanism, as the renal pelvis can be torn away from the ureter [160]. The distribution of external ureteral injuries along the ureter varies between series, but it is more common in the upper ureter [17, 161, 162].

Iatrogenic ureteral trauma can result from various mechanisms: ligation or kinking with a suture, crushing from a clamp, partial or complete transection, thermal injury, or ischaemia from devascularisation [164-166]. It usually involves damage to the lower ureter [160, 164, 165, 167]. Gynaecological operations are the commonest cause of iatrogenic trauma to the ureters (Table 4.2.1), but it may also occur in colorectal operations, especially abdominoperineal resection and low anterior resection [168]. The incidence of urological iatrogenic trauma has decreased in the last twenty years [164, 169] due to improvements in technique, instruments and surgical experience.

Risk factors for iatrogenic trauma include conditions that alter the normal anatomy, e.g. advanced malignancy, prior surgery or irradiation, diverticulitis, endometriosis, anatomical abnormalities, and major haemorrhage [164, 168, 170]. Occult ureteral injury occurs more often than reported and not all injuries are diagnosed intra-operatively. In gynaecological surgery, if routine intra-operative cystoscopy is used, the detection rate of ureteral trauma is five times higher than usually reported [170, 171].

Table 4.2.1: Incidence of ureteral injury in various procedures

Procedure	Percentage %
Gynaecological [167, 171, 172]	
Vaginal hysterectomy	0.02 – 0.5
Abdominal hysterectomy	0.03 – 2.0
Laparoscopic hysterectomy	0.2 – 6.0
Urogynaecological (anti-incontinence/prolapse)	1.7 – 3.0
Colorectal [166, 171, 173]	
Ureteroscopy [169]	
Mucosal abrasion	0.3 – 4.1
Ureteral perforation	0.2 – 2.0
Intussusception/avulsion	0 – 0.3
Radical prostatectomy [174]	
Open retropubic	0.05 – 1.6
Robot-assisted	0.05 – 0.4

4.2.3 **Diagnosis**

The diagnosis of ureteral trauma is challenging, therefore, a high index of suspicion should be maintained. In penetrating external trauma, it is usually made intra-operatively during laparotomy [175], while it is delayed in most blunt trauma and iatrogenic cases [164, 167, 176].

4.2.3.1 *Clinical diagnosis*

External ureteral trauma usually accompanies severe abdominal and pelvic injuries. Penetrating trauma is usually associated with vascular and intestinal injuries, while blunt trauma is associated with damage to the pelvic bones and lumbosacral spine injuries [161, 162]. Haematuria is an unreliable and poor indicator of ureteral injury, as it is present in only 50-75% of patients [160, 164, 177].

Iatrogenic injury may be noticed during the primary procedure, when intravenous dye (e.g. indigo carmine) is injected to exclude ureteral injury. However, it is usually noticed later, when it is discovered by subsequent evidence of upper tract obstruction, urinary fistulae formation or sepsis. The following clinical signs are characteristic of delayed diagnosis flank pain, urinary incontinence, vaginal or drain urinary leakage, haematuria, fever, uraemia or urinoma. When the diagnosis is missed, the complication rate increases [160, 163, 176]. Early recognition facilitates immediate repair and provides better outcome [172, 178].

4.2.3.2 *Radiological diagnosis*

Extravasation of contrast medium on CT is the hallmark sign of ureteral trauma. However, hydronephrosis, ascites, urinoma or mild ureteral dilation are often the only signs. In unclear cases, a retrograde or antegrade urography is the optimum standard for confirmation [164]. Intravenous pyelography, especially one-shot IVP, is unreliable in diagnosis, as it is negative in up to 60% of patients [160, 164].

4.2.4 **Prevention of iatrogenic trauma**

The prevention of iatrogenic trauma to the ureters depends upon the visual identification of the ureters and careful intra-operative dissection in their proximity [164-166]. The use of prophylactic pre-operative ureteral stent insertion assists in visualisation and palpation and is often used in complicated cases (about 4% in a large cohort) [179]. It is probably also advantageous in making it easier to detect ureteral injury [165] however, it does not decrease the rate of injury [164]. Apart from its evident disadvantages (potential complications and cost), a stent may alter the location of the ureter and diminish its flexibility [165, 173]. Routine prophylactic stenting is generally not cost-effective [165]. Another form of secondary prevention is intra-operative cystoscopy after intravenous dye injection, which can provide confirmation of ureteral patency [167]. Routine cystoscopy has minimal risks and can markedly increase the rate of ureteral injury detection [171].

4.2.5 **Management**

Management of a ureteral trauma depends on many factors concerning the nature, severity and location of the injury. Immediate diagnosis of a ligation injury during an operation can be managed by de-ligation and stent placement. Partial injuries can be repaired immediately with a stent or urine diversion by a nephrostomy tube. Stenting is helpful because it provides canalisation and may decrease the risk of stricture [164]. On the other hand, its insertion has to be weighed against potentially aggravating the severity of the ureteral injury. Immediate repair of ureteral injury is usually advisable. However, in cases of unstable trauma patients, a 'damage control' approach is preferred with ligation of the ureter, diversion of the urine (e.g. by a nephrostomy), and a delayed definitive repair [180]. Injuries that are diagnosed late are usually treated first by a nephrostomy tube with or without a stent [164].

Endo-urological treatment of delayed-diagnosed ureteral injuries by internal stenting, with or without dilatation, is the first step in most cases. It is performed either retrogradely or antegradely through a PCN, and it has a variable success rate of 14 to 89% in published series [181-183]. An open surgical repair is necessary in case of failure. The basic principles for any surgical repair of a ureteral injury are outlined in Table 4.2.2. Wide debridement is highly recommended for gunshot wound injuries due to the 'blast effect' of the injury.

4.2.5.1 *Proximal and mid-ureteral injury*

Injuries shorter than 2-3 cm can usually be managed by a primary uretero-ureterostomy [160]. When this approach is not feasible, a uretero-calycostomy should be considered. In extensive ureteral loss, a transuretero-ureterostomy is a valid option, where the proximal stump of the ureter is transposed across the midline and anastomosed to the contralateral ureter. The reported stenosis rate is 4% and intervention or revision occur in 10% of cases [184].

4.2.5.2 *Distal ureteral injury*

Distal injuries are best managed by ureteral re-implantation (uretero-neocystostomy) because the primary trauma usually jeopardises the blood supply to the distal ureter. The question of refluxing vs. non-refluxing ureteral re-implantation remains unresolved in the literature. The risk for clinically significant reflux should be weighed against the risk for ureteral obstruction.

A psoas hitch between the bladder and the ipsilateral psoas tendon is usually needed to bridge the gap and to protect the anastomosis from tension. The contralateral superior vesical pedicle may be divided to improve bladder mobility. The reported success rate is very high (97%) [184]. In extensive mid-lower ureteral injury, the large gap can be bridged with a tubularised L-shaped bladder flap (Boari flap). It is a time-consuming operation and not usually suitable in the acute setting. The success rate is reported to be 81-88% [185].

4.2.5.3 *Complete ureteral injury*

A longer ureteral injury can be replaced using a segment of the intestines, usually the ileum (ileal interposition graft). This should be avoided in patients with impaired renal function or known intestinal disease. Follow-up should include serum chemistry to diagnose hyperchloremic metabolic acidosis [186]. The long-term complications include anastomotic stricture (3%) and fistulae (6%) [187]. In cases of extensive ureteral loss or after multiple attempts at ureteral repair, the kidney can be relocated to the pelvis (autotransplantation). The renal vessels are anastomosed to the iliac vessels and a ureteral re-implantation is performed [188].

Table 4.2.2: Principles of surgical repair of ureteral injury

Debridement of necrotic tissue.
Spatulation of ureteral ends.
Watertight mucosa-to-mucosa anastomosis with absorbable sutures.
Internal stenting.
External drain.
Isolation of injury with peritoneum or omentum.

Table 4.2.3: Reconstruction option by site of injury

Site of injury	Reconstruction options
Upper ureter	Uretero-ureterostomy
	Transuretero-ureterostomy
	Uretero-calycostomy
Mid ureter	Uretero-ureterostomy
	Transuretero-ureterostomy
	Ureteral re-implantation and a Boari flap
Lower ureter	Ureteral re-implantation
	Ureteral re-implantation with a psoas hitch
Complete	Ileal interposition graft
	Autotransplantation

4.2.6 Summary of evidence and recommendations for the management of ureteral trauma

Summary of evidence	LE
Iatrogenic ureteral trauma gives rise to the commonest cause of ureteral injury.	3
Gunshot wounds account for the majority of penetrating ureteral injuries, while MVAs account for most blunt injuries.	3
Ureteral trauma usually accompanies severe abdominal and pelvic injuries.	3
Haematuria is an unreliable and poor indicator of ureteral injury.	3
The diagnosis of ureteral trauma is often delayed.	2
Pre-operative prophylactic stents do not prevent ureteral injury, but may assist in its detection.	2
Endo-urological treatment of small ureteral fistulae and strictures is safe and effective.	3
Major ureteral injury requires ureteral reconstruction following temporary urinary diversion.	3

Recommendations	LE	GR
Visually identify the ureters to prevent ureteral trauma during abdominal and pelvic surgery.	3	A*
Beware of concomitant ureteral injury in all abdominal penetrating trauma, and in deceleration-type blunt trauma.	3	A*
Use pre-operative prophylactic stents in high-risk cases.	2	B

*Upgraded following panel consensus.

4.3 Bladder Trauma

4.3.1 Classification

The AAST proposes a classification of bladder trauma, based on the extent and location of the injury [189]. Practically the location of the bladder injury is important as it will guide further management (Table 4.3.1) [190]:

- Intra-peritoneal;
- Extra-peritoneal;
- combined intra-extra-peritoneal.

Table 4.3.1: Classification of bladder trauma based on mode of action

Non-iatrogenic trauma
blunt
penetrating
Iatrogenic trauma
external
internal
foreign body

4.3.2 **Epidemiology, aetiology and pathophysiology**

4.3.2.1 *Non-iatrogenic trauma*

Motor vehicle traffic collisions are the most common cause of blunt bladder injury, followed by falls, industrial trauma/pelvic crush injuries and blows to the lower abdomen [161, 189, 191]. Between 60-90% of patients with bladder injuries caused by blunt trauma have associated pelvic fractures, and 44-68.5% of patients with bladder injuries have at least one other intra-abdominal injury [192, 193]. Pelvic fractures are associated with bladder injuries in only 3.6% of cases [161]. The incidence of extraperitoneal (34.2-86%) and intraperitoneal (14-50%) injuries varies among series [189, 192, 193]. A combination of bladder and urethral injury is present in 10-20% of cases [190, 193].

Extraperitoneal ruptures are almost always associated with pelvic fractures [191, 193]. The injury is usually caused by distortion of the pelvic ring, with shearing of the anterolateral bladder wall near the bladder base (at its fascial attachments), or by a 'counter-coup' that bursts opposite the fracture site. Occasionally, the bladder is directly perforated by a sharp bony fragment [190]. The highest risk of bladder injury was found in disruptions of the pelvic circle with displacement > 1 cm, diastasis of the pubic symphysis > 1 cm and pubic rami fractures [161, 190]. An isolated acetabular fracture is not likely to be associated with bladder injury [190, 193].

Intraperitoneal ruptures are caused by a sudden rise in intravesical pressure of a distended bladder, secondary to a blow to the pelvis or lower abdomen. The bladder dome is the weakest point of the bladder and ruptures will usually occur there [190]. Penetrating injuries, mainly gunshot wounds, are rare except in conflict regions and some urban settings [189, 194, 195]. Improvised explosive devices are at present the main cause of combat related bladder injuries in asymmetric warfare [196].

4.3.2.2 *Iatrogenic bladder trauma (IBT)*

The bladder is the urological organ that most often suffers iatrogenic injury [197]. Table 4.3.2 shows the incidence of IBT during various procedures.

Table 4.3.2: Incidence of IBT during various procedures

Procedure	Percentage (%)
External	
Obstetrics	
Caesarean delivery [198]	0.08-0.94
Gynaecology	
Abdominal radical hysterectomy [199] (malignant)	2.37
Laparoscopic radical hysterectomy [199] (malignant)	4.19
Robotic radical hysterectomy [199] (malignant)	4.38-4.59
Laparoscopic hysterectomy [200] (benign)	1
Vaginal hysterectomy [200] (benign)	0.6
Abdominal hysterectomy [200] (benign)	0.9
General surgery	
Small/large bowel procedures [201]	0.12-0.14
Rectal procedures [201]	0.27-0.41
Abdominal cytoreductive surgery [202]	4.5
Laparoscopic inguinal hernia repair [203]	0.04-0.14
Urology	
Retropubic male sling [204]	8.0-50
Laparoscopic sacrocolpopexy [205]	1.9

Burch colposuspension [206, 207]	1.0-1.2
Midurethral sling (Transobturator route) [206]	1.61
Midurethral sling (Retropubic route) [206]	4.91
Pubovaginal sling [206]	2.8
Transvaginal mesh surgery [208]	2.84
Native tissue colporrhaphy [208]	0.53
Transurethral resection of the bladder (TURB) [209, 210]	3.5-58

External IBT occurs most often during obstetric and gynaecological procedures, followed by general surgical and urological interventions [197]. Main risk factors are previous surgery, inflammation and malignancy [197].

Internal IBT mainly occurs during TURB. Reported risk factors are larger tumours, older age, pre-treated bladders (previous TURB, intravesical instillations) and location at the bladder dome [211, 212]. There is conflicting evidence whether bipolar TURB can reduce the risk of bladder perforation due to obturator jerk for tumours at the lateral wall [213, 214]. Perforations requiring intervention are rare (0.16-0.57%) [211]. Extraperitoneal perforations are more frequent than intraperitoneal perforations [212, 215].

Intravesical foreign bodies include:

- retained parts of endo-urologic equipment such as resectoscopes, ureteric stents or bladder catheters;
- forgotten pieces of surgical gauze, sutures or staples used in pelvic procedures [216];
- an unrecognised perforation or erosion of mesh used for correction of urinary incontinence or pelvic organ prolapse [217].

4.3.3 **Diagnostic evaluation**

4.3.3.1 *General evaluation*

The principal sign of bladder injury is visible haematuria [190, 191]. Non-iatrogenic bladder injury is strongly correlated with a combination of pelvic fracture and visible haematuria, and this combination is an absolute indication for further imaging [190]. Further imaging is also indicated in case of non-visible haematuria associated with either disruption of the pelvic circle with displacement > 1 cm or diastasis of the pubic symphysis > 1 cm and in case of posterior urethral injury [190]. In the absence of these absolute indications, the decision for further imaging should be based on the presence of other clinical signs and symptoms [190] which are summarised in Table 4.3.3.

Table 4.3.3: Clinical signs and symptoms of bladder injury

Signs and symptoms	Remarks
Haematuria [190, 191]	Visible = principal sign
Inability to void [190]	
Abdominal tenderness [190, 191]	
Abdominal distension [190]	In the case of urinary ascites
Uraemia and elevated creatinine level [190]	Intraperitoneal rupture => re-absorption of urea nitrogen and creatinine
Inadequate urinary output [190]	
Entrance/exit wounds at lower abdomen, perineum or buttocks [194, 218]	In penetrating injuries

Signs of external IBT are extravasation of urine, visible laceration, clear fluid in the surgical field, appearance of the bladder catheter, and blood and/or gas in the urine bag during laparoscopy [198]. Direct inspection is the most reliable method of assessing bladder integrity [197]. Intravesical instillation of methylene blue may be helpful to detect smaller lesions [219]. If bladder perforation is close to the trigone, the ureteric orifices should be inspected [197, 198].

Internal IBT is suggested by cystoscopic identification of fatty tissue, a dark space between detrusor muscle fibres, or the visualisation of bowel [209]. Signs of major perforation are the inability to distend the bladder, a low return of irrigation fluid, and abdominal distension [220].

Clinical signs and symptoms of an iatrogenic bladder trauma not recognised during surgery include haematuria, abdominal pain, abdominal distension, ileus, peritonitis, sepsis, urine leakage from the wound, decreased urinary output, and increased serum creatinine [197, 198]. An IBT during hysterectomy or caesarean delivery can be complicated by respective vesico-vaginal or vesico-uterine fistula [198, 221].

Symptoms of an intravesical foreign body include dysuria, recurrent urinary tract infection,

frequency, urgency, haematuria, and perineal/pelvic pain [217]. Bladder calculi may develop with chronic intravesical mesh exposure [217].

4.3.3.2 *Supplemental evaluation*

4.3.3.2.1 *Cystography*

Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for a suspected IBT in the post-operative setting [221, 222]. Both plain and CT cystography have a comparable sensitivity (90-95%) and specificity (100%) [191, 223]. However, CT cystography is superior in the identification of bony fragments in the bladder and bladder neck injuries as well as other abdominal injuries [190, 193].

Cystography must be performed using retrograde filling of the bladder with a minimum volume of 350 mL of dilute contrast material [221, 222].

With intraperitoneal extravasation, free contrast medium is visualised in the abdomen, highlighting bowel loops and/or outlining abdominal viscera such as the liver [224]. Extraperitoneal bladder injury is associated with flame-shaped areas of contrast extravasation in the peri-vesical soft tissues. Contrast medium in the vagina is a sign of vesico-vaginal fistula [221].

4.3.3.2.2 *Cystoscopy*

Cystoscopy is the preferred method for detection of intra-operative bladder injuries, as it may directly visualise the laceration. Cystoscopy can localise the lesion in relation to the position of the trigone and ureteral orifices [224]. A lack of bladder distension during cystoscopy suggests a large perforation.

Cystoscopy is recommended to detect perforation of the bladder (or urethra) following suburethral sling operations by the retropubic route [207]. Routine intra-operative cystoscopy during benign gynaecologic procedures significantly increases the intra-operative detection rate, however the post-operative detection rate remains unaffected [225]. Based on these findings, routine cystoscopy during benign gynaecologic procedures cannot be generally recommended, although the threshold to perform it should be low in case of suspicion of bladder injury. Cystoscopy is also preferred to diagnose a foreign body [216, 217].

4.3.3.2.3 *Excretory phase of CT or IVP*

Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is not sufficient to exclude bladder injury [190].

4.3.3.2.4 *Ultrasound*

Demonstration of intraperitoneal fluid or an extraperitoneal collection suggests intraperitoneal or extraperitoneal perforation, respectively. However, US alone is insufficient in the diagnosis of bladder trauma.

4.3.4 **Prevention**

The risk of bladder injury is reduced by emptying the bladder by urethral catheterisation in every procedure where the bladder is at risk [219, 226]. Furthermore, the balloon of the catheter can aid in identification of the bladder [219]. For tumours at the lateral wall, obturator nerve block or general anesthesia with adequate muscle relaxation can reduce the incidence of internal IBT during TURB [214]. The use of combat pelvic protection systems reduces the risk of bladder and other genito-urinary injuries due to the blast mechanism of improvised explosive devices [196, 227].

4.3.5 **Disease management**

4.3.5.1 *Conservative management*

Conservative treatment comprises clinical observation, continuous bladder drainage and antibiotic prophylaxis [212]. This is the standard treatment for an uncomplicated extraperitoneal injury due to blunt trauma [190, 193], after TURB or after other operations in which the injury was not recognised during surgery [212].

It is also an option for an uncomplicated intraperitoneal injury after TURB or after other operations in which the injury was not recognised during surgery, but only in the absence of peritonitis and ileus [210, 224]. In addition to conservative treatment, placement of an intraperitoneal drain is advocated, especially when the lesion is larger [220, 228].

On the rare occasion of a penetrating, minor and isolated extraperitoneal bladder injury, conservative management can be attempted [218, 229, 230].

4.3.5.2 *Surgical management*

The preferred method is two-layer vesicorrhaphy (mucosa-detrusor) with absorbable sutures [197, 219], although a watertight single-layer closure might be as good [193].

4.3.5.2.1 Blunt non-iatrogenic trauma

Although most extraperitoneal ruptures can be treated conservatively, bladder neck involvement, bone fragments in the bladder wall, concomitant rectal or vaginal injury or entrapment of the bladder wall will necessitate surgical intervention [190]. There is an increasing trend to treat pelvic ring fractures with open stabilisation and internal fixation with osteosynthetic material. During this procedure, an extraperitoneal rupture should be sutured concomitantly in order to reduce the risk of infection [190, 191]. Similarly, during surgical exploration for other injuries, an extraperitoneal rupture should be sutured concomitantly in order to reduce infective complications [189, 191, 192].

Intraperitoneal ruptures should always be managed by formal surgical repair [190, 193] because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death [192]. Abdominal organs should be inspected for possible associated injuries and urinomas must be drained if detected. In the absence of other intra-abdominal injuries, laparoscopic suturing of the intraperitoneal rupture is possible [191].

4.3.5.2.2 Penetrating non-iatrogenic trauma

The standard treatment is emergency exploration, debridement of devitalised bladder muscle and primary bladder repair [194, 195]. A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters [194]. In gunshot wounds, there is a strong association with intestinal and rectal injuries, requiring faecal diversion [194, 218]. Most gunshot wounds are associated with two transmural injuries (entry and exit wounds) and the bladder should be carefully checked for those two lesions [194]. As the penetrating agent (bullet, knife) is not sterile, concomitant antibiotic treatment is advised [195].

4.3.5.2.3 Iatrogenic bladder trauma

Perforations recognised intra-operatively are primarily closed [231].

For bladder injuries not recognised during surgery or for internal injuries, a distinction must be made between intraperitoneal and extraperitoneal injuries. For intraperitoneal injuries, the standard of care is surgical exploration with repair [224]. If surgical exploration is performed after TURB, the bowel must be inspected to rule out concomitant injury [211]. For extraperitoneal injuries, exploration is only needed for large perforations complicated by symptomatic extravescical collections. It requires drainage of the collection, with or without closure of the perforation [232].

If bladder perforation is encountered during mid-urethral sling or transvaginal mesh procedures, sling re-insertion and urethral catheterisation (one to two days) should be performed [233].

4.3.5.2.4 Intravesical foreign body

For perforated or eroded meshes, the intravesical portion must be removed endoscopically or by open surgery (retropubic or transvaginal). It is advised to excise the mesh at least 1 cm beyond the bladder urothelium. As this can be better accomplished with open surgery, the risk of persistent or recurrent mesh exposure is lower as compared to endoscopic removal [217]. For other types of foreign bodies, cystoscopic removal is performed and if this fails cystotomy is needed [216].

4.3.6 **Follow-up**

Continuous bladder drainage is required to prevent elevated intravesical pressure and to allow the bladder to heal [197, 234]. Conservatively treated bladder injuries (traumatic or external IBT) are followed by planned cystography scheduled to evaluate bladder healing, with catheter removal in case of absence of contrast extravasation [190]. The first cystography is planned seven to ten days after injury. In case of ongoing leakage, cystoscopy must be performed to rule out bony fragments in the bladder and, if absent, cystography is done after one week [190].

After operative repair of a simple injury in a healthy patient, the catheter can be removed after seven to ten days without need for a control cystography [234, 235]. After repair of a complex injury (trigone involvement, ureteric reimplantation) or in the case of risk factors of wound healing (e.g. use of steroids, malnutrition), control cystography is advised [234, 235].

For conservatively treated internal IBT, a catheter duration of five and seven days for extraperitoneal and intraperitoneal perforations, respectively, is proposed [212, 215].

4.3.7 **Summary of evidence and recommendations for bladder injury**

Summary of evidence	LE
The risk of bladder perforation during mid-urethral sling operations for stress urinary incontinence is lower for the obturator route compared to the retropubic route.	1a
The combination of pelvic fracture and visible haematuria is highly suggestive of bladder injury.	3

Recommendations	LE	GR
Perform cystography in case of suspicion of a iatrogenic bladder injury in the post-operative setting.	3	B
Perform cystography (conventional or computed tomography imaging) in the presence of visible haematuria and pelvic fracture.	3	B
Cystography should be performed with filling of the bladder with at least 350 mL of dilute contrast.	3	B
Use cystoscopy to rule out bladder injury after suburethral sling procedure by the retropubic route.	1a	A
Manage a blunt extraperitoneal bladder injury caused by blunt trauma conservatively, in the absence of bladder neck involvement and/or associated injuries that require surgical intervention.	3	B
Manage intraperitoneal injuries caused by blunt trauma by surgical exploration and repair.	3	A*
Manage small uncomplicated iatrogenic intraperitoneal bladder injuries conservatively.	3	B
Perform control cystography to assess bladder wall healing after repair of a simple injury in a healthy patient.	2a	C
Perform control cystography to assess bladder wall healing after repair of a complex injury or in case of risk factors for wound healing.	2a	A*

*Upgraded following panel consensus.

4.4 Urethral Trauma

4.4.1 **Epidemiology, aetiology and pathophysiology**

4.4.1.1 *Iatrogenic urethral trauma*

The most common type of urethral trauma seen in urological practice is iatrogenic, due to catheterisation, instrumentation or surgery [236, 237]. New treatment methods and applied energy sources can also injure the urethra [238].

4.4.1.1.1 Transurethral catheterisation

Iatrogenic urethral trauma usually results from improper or prolonged catheterisation and accounts for 32% of strictures. Most of these strictures affect the bulbar urethra [238, 239], while the bladder neck is rarely affected in such cases [240].

The size and type of catheter used have an important impact on urethral stricture formation. Current data indicate that silicone catheters and small-calibre Foley catheters are associated with less urethral morbidity [241] (see Figure 4.4.3). Implementing training programmes may significantly decrease the incidence of such injuries, increase patient safety and reduce the negative long-term effects [237, 242].

4.4.1.1.2 Transurethral surgery

Transurethral procedures are a common cause of iatrogenic urethral trauma. Factors that may influence the development of iatrogenic endoscopic urethral strictures include electrical dispersion generated by uni- or bipolar current and the diameter of the instruments used [243]. The incidence of urethral strictures following mono- or bipolar transurethral resection of the prostate (TURP) appear to be equal, although some data indicates that bipolar TURP has a higher urethral stricture rate when used for higher prostate volumes (> 70 mL) [244] and that bladder neck strictures are also more common when bipolar TURP is used [245].

Predisposing factors most strongly associated with stricture formation in patients undergoing TURP are increased prostate volume, prostate cancer and the surgeon's experience [246]. Meatal strictures occur as a result of a mismatch between the size of the instrument and the diameter of the urethral meatus. Bulbar strictures occur due to insufficient insulation by the lubricant, causing the monopolar current to leak. To prevent strictures, lubricant gel should be applied carefully in the urethra. The lubricant must be re-applied when the resection time is prolonged [247]. Internal urethrotomy must be performed before TURP if there are pre-existing meatal or urethral strictures [247].

There appears to be no relationship with the duration of the procedure or the method used (holmium laser or traditional TURP) on the rate of stricture formation [248].

4.4.1.1.3 Surgical treatment for prostate cancer

Urethral stricture following prostate cancer treatment can occur anywhere from the bladder neck to the urethral meatus. The rate of bladder neck constriction after radical prostatectomy varies with the definition of the stricture used and individual practice [249, 250]. Published data shows that the incidence of urethral stricture after various forms of prostate cancer therapy is 1.1-8.4%. The risk is greatest after radical prostatectomy if combined with external-beam radiation therapy. In a multivariate analysis, primary treatment type, age and obesity were found to be significant predictors for stricture development [249, 251].

Robot-assisted prostatectomy also affects urinary function and the risk of iatrogenic trauma. Iatrogenic complications involving the bladder neck account for 2.2%, similar to the stricture rate found with conventional treatment for localised prostate cancer [252].

Anastomotic stricture is a complication in conventional laparoscopic prostatectomy. If prospective studies only are taken into account, there is no significant difference in the anastomotic stricture rates comparing laparoscopic and robot-assisted radical prostatectomy [251, 253].

4.4.1.1.4 Radiotherapy for prostate cancer

The development of urinary fistulae has been reported after brachytherapy and radical prostatectomy, with incidences of 0.3-3.0% and 0-0.6%, respectively, with most fistulae involving the rectum [254, 255]. Brachytherapy is a recognised cause of strictures in patients with localised prostate cancer, as the CaPSURE study has shown [256]. Previous TURP increases the risk of stricture formation [257, 258].

4.4.1.1.5 Major pelvic surgery and cystectomy

Iatrogenic injuries to the urethra can be a complication of major pelvic procedures. Bladder and urethral catheterisation must therefore be carried out pre-operatively to prevent these complications [259]. Radical cystectomy and subsequent urinary diversion may also cause urethral trauma [260]. Table 4.4.1 lists the most common causes of urethral trauma.

Table 4.4.1: Most common causes of iatrogenic urethral trauma

Procedure	Percentage
Catheterisation	32% of iatrogenic urethral strictures (52% bulbar urethra)
Urethral instrumentation for therapy and/or diagnosis	
Treatment for prostatic disease	1.1-8.4% urethral stricture rate
Transurethral surgery (e.g. TURB/TURP)	2.2-9.8% urethral stricture rate
Radical prostatectomy (Radical prostatectomy and external-beam radiation therapy)	0.5-32% bladder neck constriction; no difference between LRP and RALP (relative risk: 1.42; 95% confidence interval for relative risk, 0.40-5.06; p = 0.59)
Radiotherapy (percutaneous or brachytherapy)	6% urethral stricture rate, 0.3-3.0% urinary fistula rate
Radical prostatectomy and external-beam radiation therapy. This combination has the greatest risk for the formation of a urethral stricture	
Cryotherapy	
High-intensity focused ultrasound	
Treatment for bladder disease	
Transurethral resection of the bladder	
Cystectomy	3.1% subneovesical obstruction, 1.2% neovesicourethral anastomotic strictures, 0.9% urethral strictures
Injury during major abdominal and pelvic operations	

TURB = transurethral resection of the bladder; TURP = transurethral resection of the prostate;
LRP = laparoscopic radical prostatectomy; RALP = robot-assisted laparoscopic radical prostatectomy;

4.4.1.2 Non-iatrogenic urethral injuries

4.4.1.2.1 Anterior urethral injuries (in males)

Different causes of anterior injuries [261] are listed in Table 4.4.2. Anterior urethral injuries are mainly caused by

blunt trauma [261-263], with the bulbar urethra being the most common site injured [263, 264]. In these bulbar injuries, which are mostly 'straddle injuries' or kicks in the perineum, the bulb is compressed against the pubic symphysis, resulting in rupture of the urethra at this site [265].

Penetrating injuries of the penile or bulbar urethra are rare and usually caused by gunshot wounds [265-270]. Depending on the affected segment, penetrating injuries are usually associated with penile, testicular and/or pelvic injuries [267, 270].

Insertion of foreign bodies is another rare cause of anterior injury. It is usually a result of autoerotic stimulation or may be associated with psychiatric disorders [266]. Penile fractures account for 10-20% of anterior injuries [266]. In up to one-third of cases, the tear extends into the corpus spongiosum and urethra [271]. Urethral instrumentation is by far the most common cause of urethral trauma in the Western world and can affect all segments of the anterior urethra [272, 273].

Table 4.4.2: Aetiology of urethral injury

Cause	Example
Blunt trauma	Vehicular accidents
	Fall astride ('straddle') e.g. on bicycle, fences, inspection covers
	Kicks in the perineum
Sexual intercourse	Penile fractures
	Urethral intraluminal stimulation
Penetrating trauma	Gunshot wounds
	Stab wounds
	Dog bites
	External impalement
	Penile amputations
Constriction bands	Paraplegia
Iatrogenic injuries	Endoscopic instruments
	Urethral catheters/dilators

4.4.1.2.2 Posterior urethral injuries (in males)

Injuries to the posterior urethra are most often related to pelvic fractures (~72%) [272, 273], which themselves are usually caused by MVAs in up to 43% of cases [18, 236, 274, 275]. Iatrogenic posterior injuries, due to irradiation or surgery to the prostate, are an increasing problem [272, 273], but appear to be less common than previously believed (3-25%) [261].

Surgically, these injuries are divided into either partial or complete ruptures. In complete ruptures, there is a gap between the disrupted ends of the urethra. The dismembered ends of the urethra retract and fibrous tissue fills the space between them [236]. There is no urethral wall in the scarred space and any lumen represents merely a fistulous tract between the urethral stumps [236]. Injury to the posterior urethra exclusively occurs in pelvic fractures with disruption of the pelvic ring [18]. The highest risk of urethral injury is in straddle fractures with a concomitant diastasis of the sacroiliac joint, followed by straddle fractures alone, and Malgaigne fractures [276]. Displaced fractures of the inferomedial pubic bone and pubic symphysis diastasis, together with their degree of displacement, are independent predictors of urethral injury [274]. Injuries of the bladder neck and prostate are rare [277] and they mostly occur at the anterior midline of both the bladder neck and prostatic urethra. It is more rare to find a complete transection of the bladder neck or an avulsion of the anterior part of the prostate [277].

Penetrating injuries of the pelvis, perineum or buttocks (mainly gunshot wounds) can also cause damage to the posterior urethra, but are extremely rare [278]. There is a high probability of associated injuries (80-90%), mainly intra-abdominal [194, 278].

Although urethral injuries themselves are not directly life-threatening [18, 261], the association with pelvic fractures and concomitant injuries of the thorax, abdomen and spine, may be life-threatening [18, 274].

Delayed morbidity of posterior urethral injuries includes strictures, incontinence and erectile dysfunction (ED), which may all have a detrimental effect on the patient's quality of life [279]. Erectile dysfunction occurs in up to 45% of patients after traumatic posterior urethral rupture [279, 280]. Strong predictors for ED are diastasis of the pubic symphysis [279-282], lateral displacement of the prostate [279, 283], a long urethral gap (> 2 cm) [279], a bilateral pubic rami fracture and a Malgaigne's fracture [279]. The assessment of sexual function and the definitive treatment (e.g. penile prosthesis) should be performed two years after the trauma because of the potential return of potency within that time [279].

4.4.1.3 Urethral injuries in females

Urethral injuries are very rare in females [262, 265]. Pelvic fractures are the main aetiology [262]. The injury is usually a partial longitudinal tear of the anterior wall associated with vaginal laceration [262, 266]. Urethral injuries in females which extend into the bladder neck may disrupt the normal continence mechanism [284].

4.4.2 Diagnosis in males and females

4.4.2.1 Clinical signs

Blood at the meatus is the cardinal sign of urethral injury [236]. The absence of it, however, does not rule out a urethral injury.

An inability to void (with a palpable distended bladder) is another classic sign and is often associated with a complete rupture [236]. In addition, haematuria and pain on urination may be present. Interestingly, lower urinary tract pain is statistically more common in men < 40 years compared to men > 60 years [282]. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on the location and extent of the trauma [261, 266]. The presentation of these clinical symptoms may be delayed (> 1 hour) [236].

Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases) [190, 285] and may reveal a 'high-riding' prostate, which is an unreliable finding [190, 236]. Failure to detect a rectal injury can cause significant morbidity and even mortality [190]. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration [190]. Another sign of urethral injury is difficulty or an inability to pass a urethral catheter [190].

A female urethral injury should be suspected from the combination of a pelvic fracture with blood at the vaginal introitus, vaginal laceration, haematuria, urethrorrhagia, labial swelling and/or urinary retention [262, 265, 266]. Vaginal examination is indicated to assess vaginal lacerations [190].

Symptoms of urethral lesions caused by improper catheterisation or instrumentation are penile and/or perineal pain (100%) and urethral bleeding (86%) [240]. Failure to accurately diagnose and treat urethral injuries may lead to significant long-term sequelae, mostly presenting as strictures [286, 287].

4.4.2.2 Further diagnostic evaluation

4.4.2.2.1 Retrograde urethrography

Retrograde urethrography is the standard diagnostic investigation for the acute evaluation of a male urethral injury [261]. A retrograde urethrography is conducted by injecting 20-30 mL of contrast material while occluding the meatus, with a balloon of a Foley catheter inflated in the fossa navicularis. Films should be taken in a 30°-oblique position, unless this is not possible because of the severity of the pelvic fractures and associated patient discomfort [261, 266]. In an unstable patient, retrograde urethrography should be postponed until the patient has been stabilised [194, 262].

A urethrogram allows for identification of the site of injury and assessment of the extent of any injury [190]. Any extravasation outside the urethra is pathognomonic for urethral injury. However, the distinction between a complete and partial rupture is not always clear [236]. A typical image for incomplete rupture shows extravasation from the urethra which occurs while the bladder is still filling. A complete rupture is suggested by massive extravasation without bladder filling [236].

The following classification of urethral injuries is based on retrograde urethrography (Table 4.4.3) [261]:

Table 4.4.3: Staging of urethral injuries*

Anterior urethra
Partial disruption
Complete disruption
Posterior urethra
Stretched but intact
Partial disruption
Complete disruption
Complex (involves bladder neck/rectum)

*According to the 2004 Consensus Panel on Urethral Trauma [261].

4.4.2.2.2 Ultrasound, computed tomography and magnetic resonance imaging

In the acute phase, US scanning is used for guiding the placement of a suprapubic catheter [261]. Computed tomography and rarely MRI are useful to evaluate concomitant injuries [261, 266].

4.4.2.2.3 Cystoscopy

Flexible cystoscopy is an option to diagnose (and manage) an acute urethral injury and may distinguish between complete- and incomplete rupture [261]. In addition, it may allow a guidewire to be passed into the bladder for early catheterisation [262, 288]. Flexible cystoscopy is also recommended above retrograde urethrography in suspected penile fracture-associated urethral injury [284, 289, 290]. In females, where the short urethra precludes adequate, radiological visualisation, urethroscopy and vaginoscopy are the diagnostic modalities of choice [261, 262]. Flexible urethroscopy also plays an important role during post-operative follow-up, as its routine use is associated with a higher detection rate of urethral stricture recurrence, compared to the use of urinary flow rates [291].

4.4.2.3 Summary

Prior to deferred management, the combination of retrograde urethrography and antegrade cysto-urethrography is standard [261]. The location and extent of the obliteration is diagnosed [261]. An MRI of the pelvis provides valuable additional information, which can help to determine the most appropriate surgical strategy [261, 283]. If the competence of the bladder neck is not clear upon antegrade cysto-urethrography, a suprapubic cystoscopy is advised [261].

Post-operative follow-up protocols include the use of retrograde urethrograms and voiding cysto-urethrograms at the time of catheter removal. Following this, urine flow charts as well as post-void residual urine, cystoscopy and urine culture, should be performed at variable intervals.

4.4.3 Disease Management

4.4.3.1 Anterior urethral injuries

Anterior urethral injuries are usually not associated with other life-threatening injuries [262, 266]. Treatment decisions are based mainly on the type of injury (blunt, penile fracture associated or penetrating).

4.4.3.1.1 Blunt anterior urethral injuries

Blunt anterior urethral injuries are associated with spongiosal contusion, which makes it more difficult to evaluate the limits of urethral debridement in the acute phase. Acute or early urethroplasty is therefore not indicated [261]. The therapeutic options are suprapubic diversion or (a trial of) early endoscopic re-alignment with transurethral catheterisation [262]. Urinary diversion is maintained for two and three weeks for partial and complete ruptures, respectively [264].

Satisfactory urethral luminal re-canalisation may occur in up to 68% after partial ruptures, but is rare after complete ruptures [264, 292].

4.4.3.1.2 Penile fracture-related anterior urethral injuries

In order to preserve erectile function, penile fractures require early exploration [265, 284, 293, 294]. The strategy consists of closing the tear in the cavernosal tunica albuginea, while the concomitant tear in the urethra is repaired at the same time [293]. In these circumstances, there is no substantial urethral tissue loss [295]. A small laceration can be repaired by simple closure, while a complete rupture requires an anastomotic repair [293, 294].

4.4.3.1.3 Penetrating anterior urethral injuries

Immediate exploration is advised, except when this is precluded by other life-threatening injuries [261]. Devitalised tissues should be debrided, although urethral and spongiosal debridement should be kept to a minimum due to the excellent vascularisation [270, 284]. For small lacerations and stab wounds, simple urethral closure might be sufficient [261]. Defects of up to 2-3 cm in length in the bulbar urethra, and up to 1.5 cm in the penile urethra, can be treated by spatulation of the urethral ends and primary anastomosis [262, 268, 270]. In the case of longer defects or apparent infection (particularly bite wounds), a staged repair with urethral marsupialisation and a suprapubic catheter is needed [268, 270]. Peri- and post-operative antibiotic treatment is also necessary [269].

4.4.3.2 Posterior urethral injuries

4.4.3.2.1 Blunt posterior urethral injuries

In posterior injuries, it is important to distinguish between complete and partial ruptures prior to treatment. The timing of the surgical intervention is classified as [261, 262]:

- immediate: < 48 hours after injury (4.4.3.2.1.1);
- delayed primary: two days to two weeks after injury (4.4.3.2.1.2);
- deferred: > three months after injury (4.4.3.2.1.3).

4.4.3.2.1.1 Immediate management

Although urinary diversion is not essential during the first hours after trauma, many prefer to perform an early urinary diversion for three main reasons [236, 262]:

- to monitor urinary output, since this is a valuable sign of the haemodynamic condition and the renal function of the patient;
- to treat symptomatic retention if the patient is still conscious;
- to minimise urinary extravasation and its secondary effects, such as infection and fibrosis.

Insertion of a suprapubic catheter is always a good solution in urgent situations [261, 284]. However, insertion of a suprapubic catheter is not without risk, especially in the unstable trauma patient where the bladder is often displaced by the pelvic haematoma or because of poor bladder filling due to haemodynamic shock or concomitant bladder injury. In these circumstances, an attempt at urethral catheterisation can be carried out by experienced hands. It is extremely unlikely that the gentle passage of a urethral catheter will do any additional damage [236, 262, 266, 272, 273, 295]. If there is any difficulty, a suprapubic catheter should be placed under US guidance and direct vision [236].

4.4.3.2.1.1.1 Partial posterior urethral rupture

Partial tears of the posterior urethra can be managed with a suprapubic or urethral catheter [284]. Urethrography should be performed at two-weekly intervals until healing has occurred [285, 296]. Injuries may heal without significant scarring or obstruction if managed by diversion alone [284]. A residual or subsequent stricture should be managed with:

- internal urethrotomy if it is short and non-obliterative;
- anastomotic urethroplasty, if it is long and dense, as is found with complete obliteration or after failed internal urethrotomy [292, 297].

4.4.3.2.1.1.2 Complete posterior urethral rupture

Acute definitive treatment options include:

- immediate re-alignment: apposition of the urethral ends over a catheter (4.4.3.2.1.1.2.1);
- immediate urethroplasty: suturing of urethral ends (4.4.3.2.1.1.2.2).

4.4.3.2.1.1.2.1 Immediate re-alignment

The aim of re-alignment is to correct severe distraction injuries rather than to prevent a stricture [284].

The reported benefits of re-alignment are:

- a lower stricture rate than with suprapubic catheter placement alone (where stricture formation is almost certain) [292, 297, 298];
- if scarring and subsequent stricture formation occurs, the restoration of urethral continuity is simplified;
- for short (< 2 cm), non-obliterative strictures, internal urethrotomy can be attempted, with a 50-90% success rate [292, 297, 299];
- for longer strictures, or in the case of failure of an internal urethrotomy, urethroplasty is required [297];
- if urethroplasty is required later, it is technically easier when the prostate and urethra are well aligned [300].

Endoscopic re-alignment is the preferred technique [262, 284]. Using a flexible/rigid cystoscope and biplanar fluoroscopy, a guidewire is placed inside the bladder. Over this, a catheter is placed into the bladder. If necessary, two cystoscopes can be used: one retrograde (per urethra) and one antegradely (suprapubic route through the bladder neck) [292, 297, 298]. The duration of catheter stay varies between four and eight weeks among series [190, 292, 297, 298].

It is important to avoid traction on the Foley balloon catheter since it can damage the remaining sphincter mechanism at the bladder neck. Concomitant bladder neck or rectal injuries or presence of bony fragments inside the bladder must be repaired immediately.

The reasons for immediate repair of bladder neck and rectal injury are:

- unrepaired bladder neck injury risks incontinence and infection of pelvic fractures;
- unrepaired rectal injury carries the obvious risk of sepsis and fistula, early exploration is indicated to evacuate contaminated haematomas and to perform colostomy if necessary.

Immediate endoscopic re-alignment can also be performed when the patient is on the operating table for other surgery. Early endoscopic re-alignment (immediate or delayed primary, see below) is also possible in a stable patient without significant concomitant injuries [297, 298].

With modern endoscopic re-alignment procedures, acceptable complication rates have been

reported for stricture formation (14-79%), incontinence (< 5%) and impotence (10-55%) [297, 298].

Differences between series in the rates of incontinence, impotence and re-stricture can be explained by differences in patient selection (severe vs. less severe trauma), a mix of partial and complete ruptures, and differences in follow-up duration. Furthermore, these differences make the comparison with other techniques difficult, especially with urethroplasty [190, 292, 297, 298].

4.4.3.2.1.1.2.2 Immediate urethroplasty

Immediate urethroplasty with suturing of the urethral ends is difficult because of poor visualisation and the inability to assess accurately the degree of urethral disruption, due to extensive swelling and ecchymosis. This might lead to extensive unjustified urethral debridement [262]. Another problem is the risk of uncontrolled bleeding following entry into the pelvic haematoma, which may result in uncontrolled re-bleeding [262]. Due to disturbingly high rates of impotence (56%), incontinence (21%) and strictures (69%) [296], immediate urethroplasty cannot be recommended and should only be done in experienced centres [301, 302].

4.4.3.2.1.1.3 Delayed primary treatment

Delayed treatment options include delayed primary re-alignment (4.4.3.2.1.2.1) and delayed primary urethroplasty (4.4.3.2.1.2.2).

4.4.3.2.1.1.3.1 Delayed primary re-alignment

In the absence of indications for immediate exploration, posterior urethral disruption can be managed in a delayed primary fashion. Delayed primary re-alignment requires the placement of a suprapubic tube at the time of initial injury, with endoscopic re-alignment performed within fourteen days (i.e. before fibrosis begins). At that time, patients are stable and most of the pelvic bleeding has resolved [296, 298]. The aim and proposed benefits of delayed primary re-alignment are the same as mentioned for immediate re-alignment. Endoscopic re-alignment is also the preferred modality.

4.4.3.2.1.1.3.2 Delayed primary urethroplasty

Delayed primary urethroplasty is performed no later than fourteen days after the initial injury i.e. before the start of the fibrotic process [303, 304]. If successful, it avoids a long period of suprapubic diversion [303]. It is restricted to stable patients with a short distraction defect, who are able to lie down in the lithotomy position [303]. Considering the limited accumulated experience with this approach, it cannot be generally recommended [303, 305, 306].

Supporters of early vs. delayed intervention state that it does not affect the outcome of an eventual subsequent urethroplasty [301, 307]. However, some authors have reported worse outcomes of subsequent urethroplasty after failed initial urethral manipulation (re-alignment or urethroplasty) [302, 303, 308]. Due to this concern and the excellent results obtained with deferred urethroplasty, early re-alignment or urethroplasty should only be selectively performed in highly experienced centres [301, 302].

4.4.3.2.1.1.4 Deferred treatment

In the case of a complete rupture, treated with an initial period of three months' suprapubic diversion, obliteration of the posterior urethra is almost inevitable [236, 296]. Treatment options for these posterior urethral strictures are deferred urethroplasty (4.4.3.2.1.3.1) and deferred endoscopic optical incision (4.4.3.2.1.3.2).

4.4.3.2.1.1.4.1 Deferred urethroplasty

Deferred urethroplasty is the procedure of choice for the treatment of posterior urethral distraction defects [284]. After three months of suprapubic diversion, the pelvic haematoma is nearly always resolved, the prostate has descended into a more normal position, the scar tissue has stabilised [303] and the patient is clinically stable and able to lie down in the lithotomy position [261, 262].

Most posterior urethral distraction defects are short and can be treated using a perineal anastomotic repair [261, 303]. The key objective of the operation is to achieve a tension-free anastomosis between two healthy urethral ends (i.e. after complete excision of any scar tissue) [284, 303].

After resection of fibrosis and spatulation of both healthy urethral ends, the gap between both ends is bridged by the so-called 'elaborated perineal approach', which is a series of consecutive manoeuvres, first described by Webster and Ramon [309] with reported success rates of 80-98% [310-314].

Most urethral stenoses are short and can be treated by mobilisation of the bulbar urethra, with or without separation of the corpora cavernosa [303]. This is in contrast to the situation in developing countries, where stenoses are more complex and where additional manoeuvres, such as inferior pubectomy and supracrural re-routing or a combined abdominoperineal approach, are needed more often [299, 311].

A number of situations may prevent the use of perineal anastomotic repair, either as an initial or as a salvage therapy. These situations probably represent < 5% of cases (Table 4.4.4) [315, 316].

Table 4.4.4: Circumstances that might preclude successful perineal anastomotic repair, either as an initial or as a salvage therapy [315, 316]

Circumstance	Alternative procedure
Distraction defects longer than 7-8 cm	A tubed interposition flap of penile or perineal skin can be used for reconstruction [317]. This is seldom required and most patients that require flap urethroplasties have previous failed repairs of posterior urethral rupture [284].
Fistulae	These might require a combined abdominoperineal approach to secure adequate closure [311].
Synchronous anterior urethral stricture	The presence of anterior urethral stricture may compromise the blood supply to the bulbar urethra following division of the bulbar arteries. These patients should be treated cautiously.
Urinary incontinence	The distal urethral sphincter mechanism can be defunctionalised by urethral distraction, so that urinary continence is maintained primarily by the proximal bladder neck sphincter. Concomitant bladder neck injury might increase incontinence and should require an abdominoperineal procedure to allow simultaneous bladder neck and urethral reconstruction [261, 284, 311].

Outcome after deferred urethroplasty is excellent with a stricture rate of around 10% [309, 318]. Deferred urethroplasty is unlikely to result in additional ED [303, 318]. Decompression of the erectile nerves after excision of the scar tissue might explain the amelioration of erectile function after urethroplasty [318]. Incontinence is rare with deferred urethroplasty (< 4%) [303] and is usually due to incompetence of the bladder neck [284, 311]. Standard therapy is a deferred urethroplasty at a minimum of three months after trauma, using a one-stage perineal approach, whenever possible.

4.4.3.2.1.1.4.2 Deferred endoscopic treatment

Cold knife or laser core-through or cut-to-the light urethrotomy for complete urethral obliteration has been described. The results of this technique are poor [319, 320] and the procedure is therefore not recommended. For short, non-obliterative strictures following re-alignment or urethroplasty, direct vision urethrotomy can be performed [312] while in other cases, urethroplasty is warranted.

4.4.3.2.2 Penetrating posterior urethral injuries

The management of penetrating posterior urethral injuries is mainly dependent on associated injuries and the clinical condition of the patient [194, 278]. If possible, immediate exploration by the retropubic route and primary repair or re-alignment can be performed [194, 278, 284]. In the case of rectal injury, a diverting colostomy is necessary [194, 278]. Life-threatening associated injuries often preclude direct urethral repair. In those cases, suprapubic diversion with delayed abdominoperineal urethroplasty is advised [194, 270, 278].

4.4.3.2.2.1 Female urethral injuries

Proximal and mid-urethral disruptions require immediate exploration and primary repair using the retropubic and transvaginal routes, respectively, with primary suturing of the urethral ends. Concomitant vaginal lacerations are repaired transvaginally at the same time [190, 262, 265, 285]. Distal urethral injuries can be managed vaginally by primary suturing and closure of the vaginal laceration [262, 285]. In all of these operations, it is advisable to use a flap (e.g. Martius) to prevent urethrovaginal fistulas [321]. Nonetheless, distal urethral injuries can be left unrepaired and hypospadiac since they do not disrupt the sphincteric mechanism [190, 262, 265, 285].

4.4.3.2.2.1.1 Iatrogenic urethral injuries

Temporary stenting with an indwelling catheter is the conventional treatment option for an acute false passage [322], although its value in minor urethral injuries is unproven. In difficult cases, catheter insertion may be assisted by cystoscopy and guidewire placement [323]. Suprapubic catheterisation is an alternative.

Endoscopic management, either with incision or resection, can successfully treat iatrogenic prostatic urethral strictures. Indwelling catheter placement or an open procedure (which is associated with increased morbidity) are alternatives [324].

Urethral lesions following radiotherapy are often more difficult to treat and may require complex reconstructive surgery [254, 255]. Section 4.4.4.1 lists the statements and recommendations regarding the iatrogenic causes of urethral trauma.

4.4.3.3 Treatment algorithms

The following algorithms are suggested for the treatment of anterior and posterior urethral injuries in men (Figures 4.4.1 and 4.4.2).

Figure 4.4.1: Management of anterior urethral injuries in men

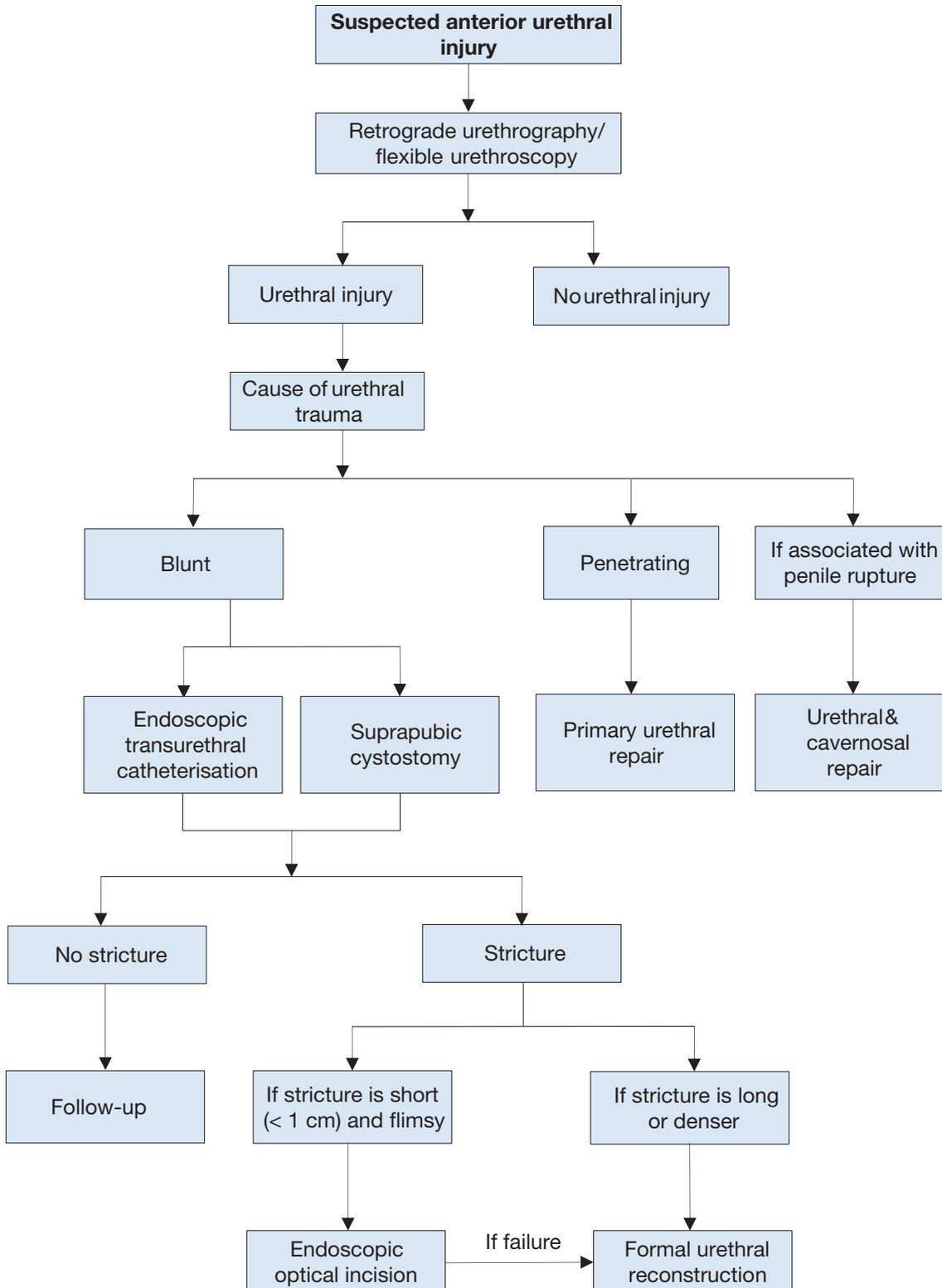


Figure 4.4.2: Management of posterior urethral injuries in men

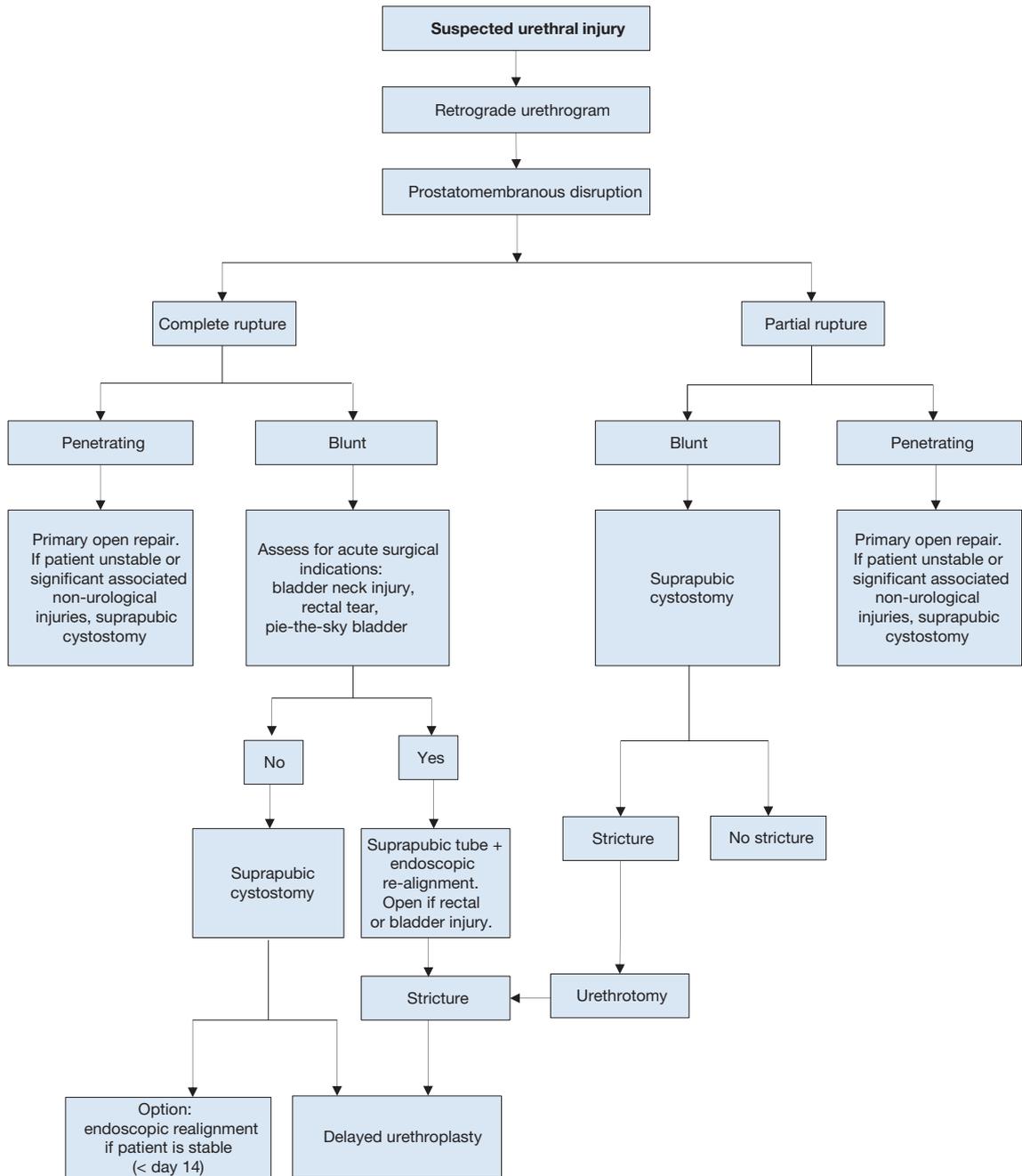


Figure 4.4.3: Treatment of iatrogenic urethral injury caused by improper insertion of a catheter

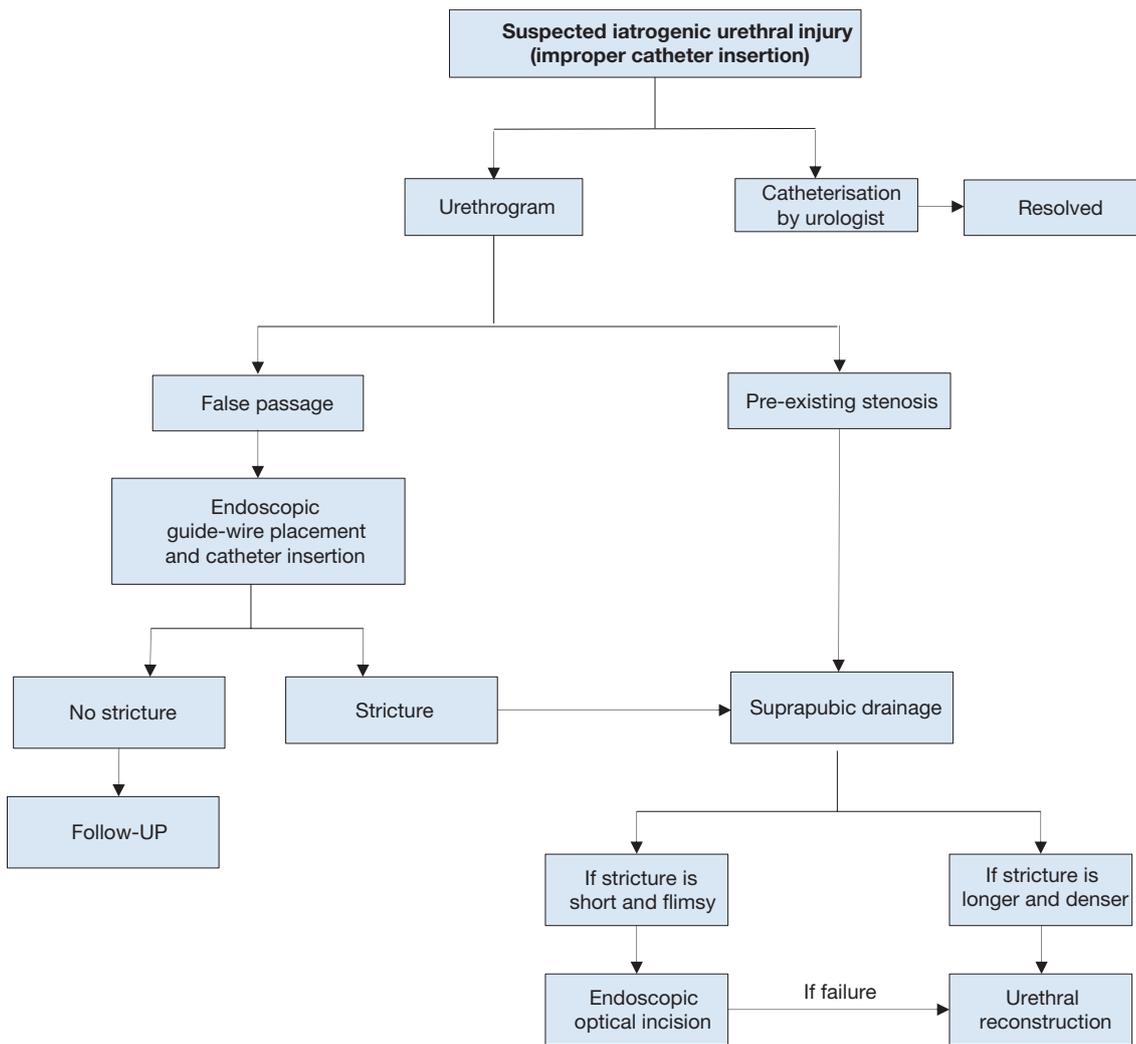
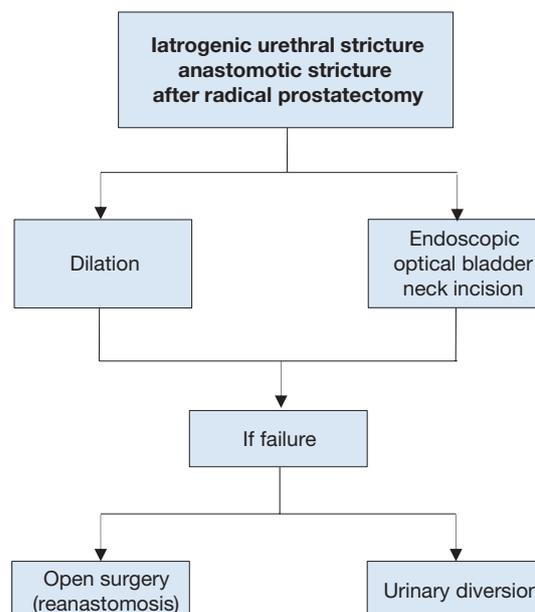


Figure 4.4.4: Treatment for stricture after radical prostatectomy



4.4.4 **Summary of evidence and recommendations for the management of urethral trauma**

Summary of evidence	LE
Blunt trauma accounts for more than 90% of urethral injuries.	3
In penile fracture, the urethra is involved in 20% of cases.	4
The male posterior urethra is injured in 4-19% of pelvic fracture cases. In industrialised societies pelvic fracture-related injuries of the posterior urethra are the most common non-iatrogenic injuries.	3
Erectile dysfunction occurs in 20-60% of patients after traumatic urethral rupture.	3

Recommendations	LE	GR
Evaluate urethral injuries with flexible cystoscopy and/or retrograde urethrography.	3	B
Treat blunt anterior urethral injuries by suprapubic diversion.	3	C
Treat partial posterior urethral ruptures by urethral or suprapubic catheterisation.	3	C
Perform early endoscopic re-alignment when feasible.	2a	B
Manage complete posterior urethral disruption with suprapubic diversion and delayed urethroplasty.	2a	A*

*Upgraded following panel consensus.

4.4.4.1 **Summary of evidence and recommendations for the management of iatrogenic urethral trauma**

Summary of evidence	LE
Iatrogenic causes are the most common type of urethral injury in Europe, and therefore the most common cause of urethral stricture formation.	2a
Implementing training programmes on urinary catheter insertion significantly improves the rate of catheter-related complications.	3
New technologies represent an additional source of urethral injury.	3

Recommendations	LE	GR
Provide appropriate training to reduce the risk of traumatic catheterisation.	3	A*
Perform urethral instrumentation when there are valid clinical indications.	4	A*
Keep duration of catheterisation to a minimum.	4	A*

*Upgraded following panel consensus.

4.5 Genital Trauma

4.5.1 Introduction and background

Genito-urinary trauma is seen in both sexes across all age groups. Of all urological injuries, 33-66% involve the external genitalia [20]. Genital trauma is much more common in males than in females, especially between the ages of 15 and 40 years. This is due to anatomical differences, increased frequency of road traffic accidents and increased participation in physical sports, war and violent crime.

Genital trauma is commonly caused by blunt injuries (80%). The risk of associated injuries to neighbouring organs (bladder, urethra, vagina, rectum and bowel) after blunt trauma is higher in females than in males. In males, blunt genital trauma frequently occurs unilaterally with only approximately 1% presenting as bilateral scrotal or testicular injuries [325].

Any kind of contact sport, without the use of necessary protective aids, may be associated with genital trauma. Off-road bicycling, motorbike riding (especially on motorbikes with a dominant petrol tank), rugby, football and hockey are all activities which are associated with blunt testicular trauma [326-329].

Penetrating injuries account for 20% of genito-urinary trauma, with 40-60% of all penetrating genito-urinary lesions involving the external genitalia [267, 330]. Thirty-five per cent of all genito-urinary gunshot wounds involve the genitalia [325]. In a recent series of wartime genito-urinary injuries, 71.5% of 361 operations involved the external genitalia - the majority caused by IEDs and other explosive ordinance, while smaller numbers of injuries were due to gunshot injuries [331]. In both males and females, penetrating genital injuries occur with other associated injuries in 70% of patients. In males, penetrating scrotal injuries affect both testes in 30% of cases compared with 1% in blunt scrotal injuries [325, 332]. Self-mutilation of the external genitalia has also been reported in psychotic patients and trans-sexuals [333]. Genital burns are rare in isolation, usually due to industrial flame or chemicals in adults, and all but the full thickness type are treated conservatively [334].

Both male and female genital piercings increase the risk for unexpected genital trauma [335]. Although there is an increased risk of Hepatitis B and C in genitally injured patients, there is no higher incidence of sexual transmitted diseases (STDs) in patients with genital piercings [335].

4.5.2 **General principles and pathophysiology**

In genital trauma, a urinalysis should be performed. The presence of visible- and/or non-visible haematuria requires a retrograde urethrogram in males. In females, flexible or rigid cystoscopy has been recommended to exclude urethral and bladder injury [336, 337]. In women with genital injuries and blood at the vaginal introitus, further gynaecological investigation is needed to exclude vaginal injuries [337]. The potential for significant injury should never be discounted in those patients who may also have blood in the vaginal vault from menstruation. Complete vaginal inspection with specula is mandatory.

4.5.2.1 *Gunshot wounds*

In patients with genitalia injured by gunshot wounds, it is very useful to have information about the causative weapon, particularly the range, calibre and type of weapon. High-velocity missiles transmit large amounts of energy to the tissues and can produce trauma to structures outside the wound track. The passage of a missile creates an expansive cavity of sub-atmospheric pressure, which then collapses and creates shear forces and induction of other foreign bodies and (usually) infected material [20].

4.5.2.2 *Bites*

4.5.2.2.1 *Animal bites*

Although animal bites are common, bites injuring the external genital are rare. Wounds are usually minor, but have a risk of wound infection. The most common bacterial infection caused by a dog bite is *Pasturella multocida*, which accounts for up to 50% of infections [338]. Other commonly involved organisms are *Escherichia coli*, *Streptococcus viridans*, *Staphylococcus aureus*, *Eikenella corrodens*, *Capnocytophaga canimorsus*, *Veillonella parvula*, *Bacteroides* and *Fusobacterium spp.* [333, 338, 339]. Antibiotics should be prescribed in accordance with local resistance patterns [340-342].

The possibility of rabies infection must be considered. If rabies infection is suspected, vaccination should be considered taking into account the geographical location, animal involved, specific nature of the wound and the type of attack (provoked/unprovoked). Besides vaccination, local wound management is an essential part of post-exposure prophylaxis. High-risk patients should be vaccinated with human rabies immunoglobulin and human diploid cell vaccine [343, 344].

4.5.2.2.2 *Human bites*

Human bites are much less common, but infection should be considered, especially in at risk groups. Since transmission of viral diseases may occur, risk assessment should be made. If appropriate, hepatitis B vaccine/immunoglobulin and/or immunodeficiency virus (HIV) post-exposure prophylaxis should be offered. For further details, see Guidelines for the Management of Human Bite Injuries [345].

4.5.2.3 *Sexual activity*

4.5.2.3.1 *Sexual intercourse*

Accidents during sexual intercourse can cause genital trauma, men of younger age are the most affected. The major pathologies are: penile fractures, strangulation and necrosis, and urethrovesical foreign bodies resulting from autoeroticism practices [346].

4.5.2.3.2 *Sexual assault*

Genital injury is often seen (42%) after sexual abuse, which must be considered when genital injuries present at any age [347]. In these cases, the examiner should be aware of the extraordinary emotional situation of the patient and the privacy of the patient should be respected. In suspicious cases, gynaecological and forensic support and advice is necessary. Swabs or vaginal smears should be taken for detection of spermatozoa [348] and local legal protocols followed closely. A thorough history and examination (in some cases under anaesthesia), photo documentation, and identification of forensic material may be important. In a recent report, only 38% of the forensic samples tested positive for an ejaculate and/or sperm. This may be due to delayed presentation or lack of vaginal/anal ejaculation [349, 350].

4.5.3 *Organ-specific genital trauma*

4.5.3.1 *Penile trauma*

4.5.3.1.1 *Blunt penile trauma*

Blunt trauma to the flaccid penis does not usually cause tearing of the tunica. In these cases, only subcutaneous haematoma with intact tunica albuginea may be seen.

4.5.3.1.1.1 Penile fracture

The most important and common presentation of blunt penile trauma is penile fracture. A recent meta-analysis on penile fractures showed that the most common causes are sexual intercourse, forced flexion (taqaandan), masturbation and rolling over in 46%, 21%, 18 % and 8.2% respectively [351]. The most common mechanism of injury is when the penis slips out of the vagina and strikes against the symphysis pubis or perineum. Sixty per cent of cases occur during consensual intercourse [352], with penile fracture more likely when the partner is on top. Penile fracture is caused by rupture of the cavernosal tunica albuginea, and may be associated with subcutaneous haematoma and lesions of the corpus spongiosum or urethra in 10-22% [353, 354].

The thickness of the tunica albuginea in the flaccid state (approximately 2 mm) decreases in erection to 0.25-0.5 mm, and is therefore more vulnerable to traumatic injury [355, 356]. Penile fracture is associated with a sudden cracking or popping sound, pain and immediate detumescence. Local swelling of the penile shaft develops quickly, due to enlarging haematoma. Bleeding may spread along the fascial layers of the penile shaft and extend to the lower abdominal wall if Buck's fascia is also ruptured. Sometimes, the rupture of the tunica may be palpable. Less severe penile injuries can be distinguished from penile fracture, as they are not usually associated with detumescence [351].

A thorough history and examination usually confirm the diagnosis, but in some cases imaging may be useful. Cavemosography, US or MRI [351, 357-359] can identify lacerations of the tunica albuginea in unclear cases [360], or provide reassurance that the tunica is intact. If a concomitant urethral injury is suspected, a retrograde urethrogram may be performed, however, flexible cystoscopy under anaesthesia during exploration/repair is more usually employed.

Subcutaneous haematoma, without associated rupture of the cavernosal tunica albuginea, does not require surgical intervention. In these cases, non-steroidal analgesics and ice-packs are recommended [361].

When a penile fracture is diagnosed, surgical intervention with closure of the tunica albuginea is recommended, it ensures the lowest rate of negative long-term sequelae and has no negative effect on the psychological well-being of the patient [362]. The approach is usually through a circumferential incision proximal to the coronal sulcus which enables complete degloving of the penis. Increasingly, local longitudinal incisions centred on the area of fracture or ventral longitudinal approaches are currently used [289]. Further localisation may be gained with a flexible cystoscopy performed prior to incision, if urethral trauma is suspected and eventually proven.

Surgical closure of the tunica should be carried out using absorbable sutures. Post-operative complications were reported in up to 20% of cases, development of plaques or nodules following surgery, post-operative curvature formation and ED occur in 13.9%, 2.8% and 1.9% of patients, respectively [351]. Conservative management of penile fracture is not recommended, as it significantly increases the rate of post-operative complications [351]. It increases complications, such as penile abscess, missed urethral disruption, penile curvature, and persistent haematoma requiring delayed surgical intervention [363]. Late complications after conservative management were fibrosis and angulations in 35% and impotence in up to 62% [352, 363].

4.5.3.2 Penetrating penile trauma

Penetrating penile trauma is rarely seen in isolation. Most cases are associated with multiple injuries. Non-operative management is recommended in small superficial injuries with intact Buck's fascia [267]. In more significant penetrating penile injuries, surgical exploration and debridement of necrotic tissue is recommended. Even in extended injuries of the penis, primary alignment of the disrupted tissues may allow for acceptable healing because of the robust penile blood supply [333].

The principles of care are debridement of devitalised tissue, with the preservation of as much viable tissues as possible, haemostasis, diversion of urine in selected cases and the removal of foreign bodies. Tissues of questionable viability may be left for subsequent definitive surgery. If a subsequent immediate or delayed repair is needed, depending on the type of injury and the extent of tissue damage, it usually takes place four to six weeks after the trauma has occurred.

The surgical approach depends upon the site and extent of the injury, but a subcoronal incision with penile degloving usually gives good exposure. Initially, a defect in the tunica albuginea should be closed after copious irrigation. If there has been too much tissue loss, the defect can be repaired either immediately or after delay with a patch (either from an autologous saphenous vein or xenograft). If a concomitant urethral injury is suspected, a pre- or peri-operative urethrogram or cystoscopy is useful to diagnose any urethral involvement, to define its position, and to decide upon the incision used.

The elasticity of genital skin means it is usually possible to manage the loss of a moderate amount of penile skin. However, management is more difficult in extensive injuries with significant skin loss. The tissue chosen for reconstruction following trauma needs to provide good coverage and must be suitable for reconstruction. Split-thickness skin grafting provides good coverage and a dependable take that is reproducible and durable. However, split-thickness grafts contract more than full-thickness grafts and their use on the penile shaft should be kept to a minimum. In accordance, McAninch *et al.* recommended the use of skin grafts with thickness of at least 0.015 inch (0.4 mm) in order to reduce the risk of contraction [333]. Full-thickness skin grafting onto the penile shaft gives less contracture, a better cosmetic appearance and more resistance to trauma during intercourse, when eventually re-established [361]. The donor site may be taken from the abdomen, buttock, thigh or axilla and is chosen according to surgeon's preference and the pattern of injury.

In cases of extensive destruction of deeper tissues, or if later prosthetic placement is being considered, skin flaps, with their secure vascular supply, can be used.

4.5.3.3 *Penile avulsion injuries and amputation*

Most injuries are self-inflicted, but some are a result of industrial accidents or assault. Acute management involves resuscitation of the patient, who may be compromised from massive blood loss, and preparation for surgical re-implantation of the penis if it has been recovered and is not too badly damaged. Surgical re-implantation should be considered for all patients and should be performed within 24 hours of amputation. If the injury occurred during a psychotic episode, early psychiatric advice and support should be sought [364].

The severed penis should be washed with sterile saline, wrapped in saline-soaked gauze, placed in a sterile bag and immersed in iced water. The penis must not come into direct contact with the ice. A pressure dressing or a tourniquet should be placed around the penile stump to prevent excessive blood loss. Re-attachment can be achieved in a non-microsurgical way, a technique which probably gives higher rates of post-operative urethral stricture and more problems with loss of sensation [365]. When operating microscopically, the corpora cavernosa and urethra are firstly aligned and repaired. Subsequently, the dorsal penile arteries, the dorsal vein and the dorsal nerves are anastomosed. The cavernosal arteries are generally too small to anastomose. The fascia and skin are closed in layers and both a urethral and a supra-pubic catheter are placed.

If the severed penis cannot be found, or is unsuitable for re-attachment, then the end should be closed as it is done in partial penectomy. Later reconstruction may be employed to lengthen the penis (e.g. suspensory ligament division and V-Y plasty, pseudo-glans formation with split-thickness skin grafting, etc). A delayed major reconstructive procedure, i.e. phalloplasty (either radial artery or pubic), is sometimes required for injuries which leave a very small or non-functioning penile stump [364].

4.5.4 **Scrotal trauma**

4.5.4.1 *Blunt scrotal trauma*

Blunt trauma to the scrotum can cause testicular dislocation, testicular haematocoele, testicular rupture and/or scrotal haematoma.

4.5.4.1.1 *Testicular dislocation*

Traumatic dislocation of the testicle rarely occurs and is most common in victims of MVAs [366-369]. Bilateral dislocation of the testes has been reported in up to 25% of cases [367]. It can be either a subcutaneous dislocation with epifascial displacement of the testis or an internal dislocation. In the latter, the testis is positioned in the superficial external inguinal ring, inguinal canal or abdominal cavity. Traumatic dislocation of the testis is treated by manual replacement and secondary orchidopexy. If primary manual reposition cannot be performed, immediate orchidopexy is indicated.

4.5.4.1.2 *Haematocoele*

Conservative management is recommended in haematocoeles smaller than three times the size of the contralateral testis [370]. In large haematocoeles, non-operative management can fail, and delayed surgery (more than three days) is often required. Patients with large haematocoeles have a higher rate of orchiectomy than patients who undergo early surgery, even in non-ruptured testes [325, 333, 371-373]. Early surgical intervention results in preservation of the testis in more than 90% of cases compared to delayed surgeries which result in orchiectomy in 45-55% of patients [373]. In addition, non-operative management is also associated with prolonged hospital stays. Therefore, large haematocoeles should be treated surgically, irrespective of the presence of testicular contusion or rupture. At the very least, the blood clot should be evacuated from the tunica vaginalis sac to relieve disability and hasten recovery. Patients initially treated non-operatively may eventually need delayed surgery if they develop infection or undue pain.

4.5.4.1.3 Testicular rupture

Testicular rupture is found in approximately 50% of cases of direct blunt scrotal trauma [373]. It may occur under intense, traumatic compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea of the testis. A force of approximately 50 kg is necessary to cause testicular rupture [374]. Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting. The hemiscrotum is tender, swollen, and ecchymotic. The testis itself may be difficult to palpate.

Ultrasound should be performed to determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture [375-383]. However, the literature is contradictory as to the usefulness of US compared to clinical examination alone. Some studies have reported convincing findings with a specificity of up to 98.6% [356]. Others reported poor specificity (78%) and sensitivity (28%) for the differentiation between testicular rupture and haematocele, while accuracy is as low as 56% [376]. Colour Doppler-duplex US may provide useful information when used to evaluate testicular perfusion. If scrotal US is inconclusive, testicular CT or MRI may be helpful [384]. However, these techniques did not specifically increase the detection rates of testicular rupture. It is therefore essential to surgically explore equivocal patients whenever imaging studies cannot definitively exclude testicular rupture. This involves exploration with evacuation of blood clots and haematoma, excision of any necrotic testicular tubules and closure of the tunica albuginea, usually with running absorbable sutures (e.g. 3/0 Vicryl).

4.5.4.2 Penetrating scrotal trauma

Penetrating injuries to the scrotum require surgical exploration with conservative debridement of non-viable tissue. Depending on the extent of the injury, primary reconstruction of the testis and scrotum can usually be performed. In complete disruption of the spermatic cord, re-alignment without vaso-vasostomy may be considered if surgically feasible [385]. Staged secondary microsurgical vaso-vasostomy can be performed after rehabilitation, although only a few cases have been reported [385]. If there is extensive destruction of the tunica albuginea, mobilisation of a free tunica vaginalis flap can be performed for testicular closure. If the patient is unstable or reconstruction cannot be achieved, orchiectomy is then indicated.

Prophylactic antibiotics are recommended after scrotal penetrating trauma, although data to support this approach is lacking. Tetanus prophylaxis is mandatory. Post-operative complications were reported in 8% of patients who underwent testicular repair after penetrating trauma [267].

Extended laceration of scrotal skin requires surgical intervention for skin closure. Due to the elasticity of the scrotum, most defects can be primarily closed, even if the lacerated skin is only minimally attached to the scrotum [333]. Local wound management with extensive initial wound debridement and washout is important for scrotal convalescence. In the case of extensive loss of genital tissue, e.g. IED blast injury, complex and staged reconstructive surgical procedures are often required [331].

4.5.5 Genital trauma in females

In females with blunt trauma to the external genitalia, imaging of the pelvis with US, CT, or MRI should be performed since additional injuries and extensive intra-pelvic haematomas are frequently expected [337, 348].

4.5.5.1 Coital injury of the female genital tract

Consensual sexual intercourse can lead to genital trauma in women. Up to 35% of all genital injuries in women are sustained during their first sexual contact. The majority of women present with bleeding and pain. The most frequently found injuries are lacerations. These lesions can be treated with a simple suture under local anesthesia [386].

4.5.5.2 Blunt vulvar injuries

Blunt trauma to the vulva is rarely reported and usually presents as a large haematoma. The incidence of traumatic vulvar haematomas after vaginal deliveries has been reported as 1 in 310 deliveries [387]. Although blunt trauma to the female external genitalia is rarely reported, the presence of a vulvar haematoma is closely related to an increased risk of associated vaginal, pelvic or abdominal injuries. Goldman *et al.* reported that blunt injuries of the vulva and vagina were associated with pelvic trauma in 30%, after consensual intercourse in 25%, following sexual assault in 20%, and other blunt trauma in 15% [336].

Blunt vulvar or perineal trauma may be associated with voiding problems and bladder catheterisation is usually required. Vulvar haematomas usually do not require surgical intervention, although they can cause a significant blood loss, which sometimes even requires blood transfusion. Data are scarce [388], but in haemodynamically stable women, non-steroidal anti-inflammatory medication and cold packs are generally successful. Yet, in

cases of massive vulvar haematoma and haemodynamically unstable patients, surgical intervention with lavage and drainage is sometimes indicated [389].

Although antibiotics are often recommended after major vulvar trauma, there is no data to support this approach. It is important to emphasise that vulvar haematoma and/or blood at the vaginal introitus are indications for vaginal exploration under sedation or general anaesthesia. The aim is to identify possible associated vaginal and/or rectal injuries [337]. Flexible or rigid cystoscopy has been recommended to exclude urethral and bladder injury [336, 337]. In the case of vulvar laceration, suturing after conservative debridement is indicated. If there are associated injuries to the vagina, these can be repaired immediately by primary suturing.

4.5.6 Summary of evidence and recommendations for the management of genital trauma

Summary of evidence	LE
Most genital injuries, in males and females, are caused by blunt trauma.	3

Recommendations	LE	GR
Treat penile fractures surgically, with closure of tunica albuginea.	2a	B
Explore the injured testis in all cases of testicular rupture and in those with inconclusive ultrasound findings.	3	B

5. POLYTRAUMA, DAMAGE CONTROL AND MASS CASUALTY EVENTS

5.1 Introduction

Urological trauma is often associated with significant and higher priority injuries in the polytraumatised patient [390]. Lessons from civilian trauma networks, the battlefield, and mass casualty events have led to many advances in general trauma care [391, 392]. These include the widespread acceptance of damage control principles, trauma centralisation and recognition of the value of dedicated trauma teams. Urologists need to understand their role in the context of polytrauma with the ultimate aims of improving survivability and decreasing morbidity in these patients.

5.1.1 The development of major trauma centres

Multidisciplinary management of trauma patients has been shown to improve outcomes [393]. Major trauma patients initially managed in local hospitals are 1.5-5 times more likely to die than patients transported directly to specialist trauma centres. The re-organisation of care to these centres has been shown to reduce mortality by 25% and length of stay by four days [391]. Major trauma centres, which are expected to provide senior-led resuscitative trauma teams, dedicated trauma theatres, input from all major surgical specialties and interventional radiologists, have therefore been established worldwide. Urologists have an important role to play in this process [394].

5.1.1.1 Recommendations for polytrauma management

Recommendations	LE	GR
Manage polytrauma patients in designated major trauma centres within a trauma network.	3	A*
Involve urologists in cases of associated urological injury.	3	A*

*Upgraded following panel consensus.

5.2 Damage control

Damage control is a life-saving strategy for severely injured patients that recognises the consequences of the lethal triad of trauma, i.e. hypothermia, coagulopathy and acidosis [395-397].

It is a prioritised three-phase approach:

- the first phase consists of rapid control of haemorrhage and wound contamination;

- the second phase involves resuscitation in the intensive care unit (ICU), with the goal of restoring normal temperature, coagulation, and tissue oxygenation;
- the third stage involves definitive surgery when more time-consuming reconstructive procedures are performed in the stabilised patient [398].

Identifying which patients benefit from the damage control mode requires critical decision-making by the trauma team leader. Prior preparedness and regular communication between the surgical, critical care and anaesthetic teams are vital [399]. Damage control principles have been successfully adopted in the context of civilian mass casualty events, military field surgery, and initial treatment in rural areas with long-range transfers [396, 400].

5.3 Management principles: polytrauma and associated urological injury

Urologists are often asked for advice in polytrauma patients, some of whom might be in a damage control phase of management. Fortunately, the management of urological trauma often involves the use of temporary measures, followed by later definitive surgery, which fits in well with these principles. In the polytrauma setting, the urologist will usually work alongside the general/trauma surgeon. Procedures should be directed at the rapid control of bleeding, debridement of dead and devitalised tissue, and minimising urinary extravasation by simple diversionary measures. Complex reconstructive procedures, including organ preservation, are preferably delayed.

Examples where urological input is required in the polytraumatised patient include:

- haemodynamically unstable patients with suspected intra-abdominal bleeding, who are transferred urgently to the operating theatre without any pre-operative imaging;
- stable patients with suspected renal injuries-penetrating trauma to the upper abdomen/flanks/lower chest, or blunt abdominal trauma and visible haematuria;
- patients with suspected urethral or bladder injury associated with pelvic fractures; blood at the urethral meatus and/or the inability to void;
- external genitalia injury associated with penetrating trauma (intra-abdominal injury).

5.3.1 Summary of evidence and recommendations for management principles of polytrauma and associated urological injury

Summary of evidence	LE
Damage control principles govern the management of severely injured polytrauma patients.	4

Recommendation	LE	GR
Follow damage control principles in the management of severely injured polytrauma patients.	4	A*

*Upgraded following panel consensus.

5.4 Urological injury management in polytrauma

5.4.1 Renal injury

The incidence of multi-organ injury is high in penetrating trauma [32]. Most of these injuries can be managed without surgical exploration [29]. Renal exploration is required to control life-threatening bleeding [401]. The preservation of viable renal parenchyma is a secondary goal, with time-consuming renal reconstruction delayed until the patient is optimised [112].

At laparotomy, it is considered best practice not to explore the injured kidney if there is no active haemorrhage, even if delayed exploration is then necessary [79]. In unstable patients, packing the renal fossa and transferring the patient to the surgical intensive care unit is the option of choice for damage control. A planned second-look laparotomy is then performed [180]. However, in patients with significant ongoing haemorrhage, speedy nephrectomy is required. It is recommended that the contralateral kidney should at least be palpated prior to nephrectomy [402].

In patients who are packed temporarily and who become sufficiently stable in the intensive setting, radiological assessment allows definitive management to begin. Computed tomography allows the kidney injury to be graded, documents the presence of a contralateral kidney, and helps to determine whether or not intervention (radiological or surgical) is necessary.

In patients who are haemodynamically unstable after the initial acute-damage-control laparotomy, or in patients with deteriorating haemodynamic parameters (indicating ongoing or delayed bleeding), the management options are angiographic embolisation of the bleeding kidney or re-operation. This decision should be made according to:

- the status of the patient;
- the presence of associated injuries (stapled bowel, packed liver or spleen), which may need re-operation irrespective of the renal injury;
- the availability of angioembolisation.

5.4.1.1 Renal preservation

Haemostatic techniques, many of which were developed for hepatic surgery and splenic trauma, can be used to control renal parenchymal bleeding. These techniques are not consistent with damage control principles and should only be considered in the rare casualty situation of a solitary kidney or bilateral renal injury. These techniques are outlined below:

- mattress sutures through the parenchyma, i.e. renorrhaphy [180];
- haemostatic agents, i.e. combined acellular matrix and fibrin sealants [114];
- absorbable mesh kidney bags to maintain contact between renal parenchymal fragments [107];
- intra-operative drain left *in situ* to collect any urine that leaks following organ salvage.

5.4.1.2 Recommendations for the management of renal injury

Recommendations	LE	GR
Manage life-threatening bleeding from renal injury by urgent nephrectomy.	4	B*
Manage profuse non-arterial bleeding by renal packing as a damage control measure.	4	B*
Use angioembolisation as an effective haemostatic measure.	4	B*

*Upgraded based on panel consensus

5.4.2 Ureteral injury

Ureteral injuries are primarily associated with penetrating intra-abdominal injury; although rapid deceleration injuries can also result in ureteropelvic disruption [164]. A high index of suspicion is required as these injuries are quite commonly missed [403]. The results of immediate ureteral reconstruction are generally satisfactory, but this is time-consuming and may not be appropriate in the polytraumatised patient. Diagnostic procedures, such as on-table IVP or retrograde ureteropyelography to evaluate ureteral injuries are also not recommended in this setting.

If a ureteral injury is suspected but not clearly identified, a drain should be sited. If urine leaks post-operatively, a nephrostomy should be arranged. If a partial ureteral tear is identified (less than half a circumference) and the ureter is otherwise healthy, a double J-stent may be inserted over a guide wire through the tear, and the tear quickly closed with fine interrupted absorbable stitches.

When complete ureteral injuries are identified, definitive repair should not be performed. Dissection of the ureteral stumps should be avoided as it interferes with the blood supply. Temporary measures to control urine spillage should be performed:

- a single J or 8 French feeding tube is inserted into the ureter;
- the end of the disrupted proximal ureter is secured over the tube, which is exteriorised and secured to the skin.

The distal ureteral stump does not need to be ligated and any unnecessary manipulation should be avoided. Intra-operative placement of a nephrostomy tube is time-consuming and should be avoided [112, 180]. Tying off the injured ureteral segment and inserting a percutaneous nephrostomy post-operatively is a viable alternative [404]. Rarely, in cases with severe associated injuries of the ipsilateral kidney, nephrectomy is required.

5.4.2.1 *Recommendations for the management of ureteral injury*

Recommendations	LE	GR
Rule out ureteral injury in penetrating abdominal trauma.	4	A*
Treat ureteral injury with 'tube' urinary diversion if repair is not performed.	4	C

*Upgraded following panel consensus.

5.4.3 **Bladder trauma**

In the acute polytrauma setting, a bladder injury should be treated with bladder drainage by a suprapubic and/or a urethral catheter. Later, definitive treatment can follow as necessary [405]. Ideally, large intraperitoneal bladder ruptures (often associated with unstable pelvic fractures) should be closed primarily and drained, as this will cope with both haemorrhage control and urinary contamination.

Examples of temporary measures that may be necessary include:

- the placement of externalised ureteral stents to provide external urinary drainage in extensive bladder rupture [180];
- packing and/or arteriography and selective embolisation in unstable patients with severe bladder haemorrhage [180];
- the placement of a pelvic suction drain for urinary evacuation [180].

5.4.3.1 *Recommendations for the management of bladder trauma and urethral injury*

Recommendations	LE	GR
Provide urinary drainage by either the suprapubic or urethral route.	3	A

5.4.4 **Urethral injury**

Urethral injury of any kind is not life-threatening, but the associated injuries are often severe. In this situation, wherever the location or extent of injury, drainage through a suprapubic or urethral catheter should be obtained without prior imaging [261].

5.4.5 **External genital injury**

Traditionally, traumatic injuries of the external genitalia have a low priority and management is often deferred [406]. In the polytraumatised patient, the management of these injuries should be guided by the principles of haemorrhage control, debridement and urinary diversion (via a catheter). Delayed organ conservation is possible, particularly in testicular injury [407].

Temporary damage control measures that might be applicable include:

- compression dressing of the penis [180];
- packing of penetrating testicular injuries;
- tampons for vulvar lacerations.

5.5 **Mass casualty events**

A mass casualty event is one in which the number of injured people is significantly higher than the number of available healthcare providers [408]. A mass casualty disaster does not therefore necessarily involve a large number of victims, but it is related to the disproportion between the number of victims and the size of the medical team available [409, 410].

There are little published data on the best way in which to handle these events. However, recent developments in both the military and civilian settings have led to greater survivability following major trauma [411]. Triage, communication and preparedness are important components for a successful response.

Potential mass casualty events include:

- transportation systems accidents, e.g. road traffic, aircraft, shipping, railways;
- natural disasters, e.g. earthquakes, hurricanes, floods, tsunamis;
- industry, e.g. chemical spills, factory explosions and fires;
- civilian terrorism.

5.5.1 Triage

Triage after mass casualty events is difficult and involves difficult moral and ethical considerations. Disaster triage requires differentiation of the few critically injured individuals who can be saved by immediate intervention from the many others with non-life-threatening injuries for whom treatment can be delayed. The ethical dilemmas that arise are primarily caused by having to decide who should be actively treated, or subsequently whether to stop treatment, because of injuries deemed un-survivable or incompatible with survival in the home environment.

Triage sorts patients into four groups [412, 413]:

1. Patients with life-threatening injuries that require immediate intervention, presenting with airway compromise, breathing failure and/or circulatory compromise from ongoing external haemorrhage.
2. Patients with severe but non-life-threatening injuries, in whom treatment can be acceptably delayed, including those with major fractures, vascular injuries of the limbs and large soft tissue wounds.
3. 'Walking wounded', i.e. casualties with minimal injuries.
4. Patients who are so severely injured that treatment would require allocation of resources and time that would deny timely care to other patients with greater survivability. These patients are given minimal or no treatment, and are re-evaluated when resources become available. There is no absolute definition for this group because triage is individualised, according to the number and severity of casualties related to the available resources. The decision to implement this category is decided when sufficient information of the incident is available and is made at the highest level possible.

Triage should be performed at each stage from the pre-hospital setting to the emergency department and repeated as the clinical situation evolves. Ultimately, the individual in charge is responsible for directing specialty surgical teams, including urologists, and assigning them responsibility for specific patients as dictated by the specific injuries.

5.5.2 Urological role in the mass casualty setting

Urological consultations during a mass casualty scenario should follow the principles outlined below:

1. Rule out under-triage by the surgeon in charge, and perform a rapid primary survey of every patient.
2. Avoid unnecessary imaging procedures such as CT scans and retrograde urethrography. These procedures should be performed later, after re-evaluation of the patient, and after mass casualty protocols have been suspended.
3. Treat unstable patients who are to have surgery using damage control principles.
4. Stable patients should be transferred to the surgical ward without imaging procedures. Re-evaluate if there is any change in their haemodynamic status, or when possible as dictated by the constraints of the mass casualty event.
5. 'Minimal acceptable' treatment for all urological injuries should be performed in order to transfer patients to the surgical wards and are outlined above in the Section 5.4 Urological injury management in polytrauma.

6. REFERENCES

1. Tekgül, S., *et al.* EAU Guidelines on Paediatric Urology 2017. In: EAU Guidelines Edn. Presented at the EAU Annual Congress London 2017, European Association of Urology, Guidelines Office, Arnhem, The Netherlands.
<https://uroweb.org/guideline/paediatric-urology/>
2. Martinez-Pineiro, L., *et al.* EAU Guidelines on Urethral Trauma. *Eur Urol*, 2010. 57: 791.
<http://www.ncbi.nlm.nih.gov/pubmed/20122789>
3. Summerton, D.J., *et al.* EAU guidelines on iatrogenic trauma. *Eur Urol*, 2012. 62: 628.
<http://www.ncbi.nlm.nih.gov/pubmed/22717550>
4. Lumen, N., *et al.* Review of the current management of lower urinary tract injuries by the EAU Trauma Guidelines Panel. *Eur Urol*, 2015. 67: 925.
<http://www.ncbi.nlm.nih.gov/pubmed/25576009>
5. Serafetinides, E., *et al.* Review of the current management of upper urinary tract injuries by the EAU Trauma Guidelines Panel. *Eur Urol*, 2015. 67: 930.
<http://www.ncbi.nlm.nih.gov/pubmed/25578621>

6. Sujenthiran, A. Is conservative/minimally-invasive management of grade 4-5 renal trauma safe and effective compared with open surgical exploration? PROSPERO 2016.
https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016035255
7. Elshout P-J., V.E., Serafetinidis E. What are the comparative outcomes of early endoscopic realignment versus suprapubic diversion alone for pelvic fracture related urethral injuries?. PROSPERO International prospective register of systematic reviews, 2015.
https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027974
8. Phillips, B., *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
9. Soreide, K. Epidemiology of major trauma. *Br J Surg*, 2009. 96: 697.
<http://www.ncbi.nlm.nih.gov/pubmed/19526611>
10. Middleton, P., The trauma epidemic. In: Major Trauma Smith, J., Greaves, I., Porter, K. (2010) Oxford University Press: Oxford.
11. Thornley, S., *et al.* Alcohol intake, marijuana use, and sleep deprivation on the risk of falls occurring at home among young and middle-aged adults: a case-crossover study. *N Z Med J*, 2014. 127: 32.
<http://www.ncbi.nlm.nih.gov/pubmed/25447247>
12. Bergen, G., *et al.* Vital signs: health burden and medical costs of nonfatal injuries to motor vehicle occupants - United States, 2012. *MMWR Morb Mortal Wkly Rep*, 2014. 63: 894.
<http://www.ncbi.nlm.nih.gov/pubmed/25299606>
13. Baverstock, R., *et al.* Severe blunt renal trauma: a 7-year retrospective review from a provincial trauma centre. *Can J Urol*, 2001. 8: 1372.
<http://www.ncbi.nlm.nih.gov/pubmed/11718633>
14. Meng, M.V., *et al.* Renal trauma: indications and techniques for surgical exploration. *World J Urol*, 1999. 17: 71.
<http://www.ncbi.nlm.nih.gov/pubmed/10367364>
15. Bruce, L.M., *et al.* Blunt renal artery injury: incidence, diagnosis, and management. *Am Surg*, 2001. 67: 550.
<http://www.ncbi.nlm.nih.gov/pubmed/11409803>
16. Kuan, J.K., *et al.* Renal injury mechanisms of motor vehicle collisions: analysis of the crash injury research and engineering network data set. *J Urol*, 2007. 178: 935.
<http://www.ncbi.nlm.nih.gov/pubmed/17632156>
17. Pereira, B.M., *et al.* A review of ureteral injuries after external trauma. *Scand J Trauma Resusc Emerg Med*, 2010. 18: 6.
<http://www.ncbi.nlm.nih.gov/pubmed/20128905>
18. Bjurlin, M.A., *et al.* Genitourinary injuries in pelvic fracture morbidity and mortality using the National Trauma Data Bank. *J Trauma*, 2009. 67: 1033.
<http://www.ncbi.nlm.nih.gov/pubmed/19901665>
19. Dixon, C.M., Diagnosis and acute management of posterior urethral disruptions. In: Traumatic and reconstructive urology, McAninch, J.W. (1996) WB Saunders: Philadelphia.
20. Brandes, S.B., *et al.* External genitalia gunshot wounds: a ten-year experience with fifty-six cases. *J Trauma*, 1995. 39: 266.
<http://www.ncbi.nlm.nih.gov/pubmed/7674395>
21. Moore, E.E., *et al.* Organ injury scaling: spleen, liver, and kidney. *J Trauma*, 1989. 29: 1664.
<http://www.ncbi.nlm.nih.gov/pubmed/2593197>
22. Wutzler, S., *et al.* Association of preexisting medical conditions with in-hospital mortality in multiple-trauma patients. *J Am Coll Surg*, 2009. 209: 75.
<http://www.ncbi.nlm.nih.gov/pubmed/19651066>
23. Shoko, T., *et al.* Effect of pre-existing medical conditions on in-hospital mortality: analysis of 20,257 trauma patients in Japan. *J Am Coll Surg*, 2010. 211: 338.
<http://www.ncbi.nlm.nih.gov/pubmed/20800190>
24. Cline, K.J., *et al.* Penetrating trauma to the male external genitalia. *J Trauma*, 1998. 44: 492.
<http://www.ncbi.nlm.nih.gov/pubmed/9529176>
25. Centers for Disease Control and Prevention, Tetanus wound management.
<https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/tetanus.pdf>
26. McAninch, J.W. Genitourinary trauma. *World J Urol*, 1999. 17: 65.
<http://www.ncbi.nlm.nih.gov/pubmed/10367362>
27. Wessells, H., *et al.* Renal injury and operative management in the United States: results of a population-based study. *J Trauma*, 2003. 54: 423.
<http://www.ncbi.nlm.nih.gov/pubmed/12634519>

28. Hurtuk, M., *et al.* Trauma surgeons practice what they preach: The NTDB story on solid organ injury management. *J Trauma*, 2006. 61: 243.
<http://www.ncbi.nlm.nih.gov/pubmed/16917435>
29. Santucci, R.A., *et al.* The literature increasingly supports expectant (conservative) management of renal trauma--a systematic review. *J Trauma*, 2005. 59: 493.
<http://www.ncbi.nlm.nih.gov/pubmed/16294101>
30. Santucci, R.A., *et al.* Evaluation and management of renal injuries: consensus statement of the renal trauma subcommittee. *BJU Int*, 2004. 93: 937.
<http://www.ncbi.nlm.nih.gov/pubmed/15142141>
31. Sangthong, B., *et al.* Management and hospital outcomes of blunt renal artery injuries: analysis of 517 patients from the National Trauma Data Bank. *J Am Coll Surg*, 2006. 203: 612.
<http://www.ncbi.nlm.nih.gov/pubmed/17084321>
32. Kansas, B.T., *et al.* Incidence and management of penetrating renal trauma in patients with multiorgan injury: extended experience at an inner city trauma center. *J Urol*, 2004. 172: 1355.
<http://www.ncbi.nlm.nih.gov/pubmed/15371841>
33. Najibi, S., *et al.* Civilian gunshot wounds to the genitourinary tract: incidence, anatomic distribution, associated injuries, and outcomes. *Urology*, 2010. 76: 977.
<http://www.ncbi.nlm.nih.gov/pubmed/20605196>
34. Shariat, S.F., *et al.* Evidence-based validation of the predictive value of the American Association for the Surgery of Trauma kidney injury scale. *J Trauma*, 2007. 62: 933.
<http://www.ncbi.nlm.nih.gov/pubmed/17426551>
35. Santucci, R.A., *et al.* Validation of the American Association for the Surgery of Trauma organ injury severity scale for the kidney. *J Trauma*, 2001. 50: 195.
<http://www.ncbi.nlm.nih.gov/pubmed/11242281>
36. Dugi, D.D., 3rd, *et al.* American Association for the Surgery of Trauma grade 4 renal injury substratification into grades 4a (low risk) and 4b (high risk). *J Urol*, 2010. 183: 592.
<http://www.ncbi.nlm.nih.gov/pubmed/20018329>
37. Buckley, J.C., *et al.* Revision of current American Association for the Surgery of Trauma Renal Injury grading system. *J Trauma*, 2011. 70: 35.
<http://www.ncbi.nlm.nih.gov/pubmed/21217478>
38. Cachecho, R., *et al.* Management of the trauma patient with pre-existing renal disease. *Crit Care Clin*, 1994. 10: 523.
<http://www.ncbi.nlm.nih.gov/pubmed/792273629>
39. Cozar, J.M., *et al.* [Management of injury of the solitary kidney]. *Arch Esp Urol*, 1990. 43: 15.
<http://www.ncbi.nlm.nih.gov/pubmed/2331159>
40. Sebastia, M.C., *et al.* Renal trauma in occult ureteropelvic junction obstruction: CT findings. *Eur Radiol*, 1999. 9: 611.
<http://www.ncbi.nlm.nih.gov/pubmed/10354870>
41. Buchberger, W., *et al.* [Diagnosis and staging of blunt kidney trauma. A comparison of urinalysis, i.v. urography, sonography and computed tomography]. *Rofo*, 1993. 158: 507.
<http://www.ncbi.nlm.nih.gov/pubmed/8507839>
42. Carroll, P.R., *et al.* Renovascular trauma: risk assessment, surgical management, and outcome. *J Trauma*, 1990. 30: 547.
<http://www.ncbi.nlm.nih.gov/pubmed/2342137>
43. Eastham, J.A., *et al.* Radiographic evaluation of adult patients with blunt renal trauma. *J Urol*, 1992. 148: 266.
<http://www.ncbi.nlm.nih.gov/pubmed/1635113>
44. Schmidlin, F.R., *et al.* The higher injury risk of abnormal kidneys in blunt renal trauma. *Scand J Urol Nephrol*, 1998. 32: 388.
<http://www.ncbi.nlm.nih.gov/pubmed/9925001>
45. Chandhoke, P.S., *et al.* Detection and significance of microscopic hematuria in patients with blunt renal trauma. *J Urol*, 1988. 140: 16.
<http://www.ncbi.nlm.nih.gov/pubmed/3379684>
46. Heyns, C.F. Renal trauma: indications for imaging and surgical exploration. *BJU Int*, 2004. 93: 1165.
<http://www.ncbi.nlm.nih.gov/pubmed/15142132>
47. Sheth, S., *et al.* American College of Radiology, Appropriateness Criteria: Renal Trauma. 2012.
<https://acsearch.acr.org/docs/69373/Narrative/>
48. Morey, A.F., *et al.* Urotrauma: AUA guideline. *J Urol*, 2014. 192: 327.
<http://www.ncbi.nlm.nih.gov/pubmed/24857651>

49. McCombie, S.P., *et al.* The conservative management of renal trauma: a literature review and practical clinical guideline from Australia and New Zealand. *BJU Int*, 2014. 114 Suppl 1: 13.
<http://www.ncbi.nlm.nih.gov/pubmed/25124459>
50. Poletti, P.A., *et al.* Blunt abdominal trauma: does the use of a second-generation sonographic contrast agent help to detect solid organ injuries? *AJR Am J Roentgenol*, 2004. 183: 1293.
<http://www.ncbi.nlm.nih.gov/pubmed/15505293>
51. Valentino, M., *et al.* Blunt abdominal trauma: emergency contrast-enhanced sonography for detection of solid organ injuries. *AJR Am J Roentgenol*, 2006. 186: 1361.
<http://www.ncbi.nlm.nih.gov/pubmed/16632732>
52. Korner, M., *et al.* Current Role of Emergency US in Patients with Major Trauma. *Radiographics*, 2008. 28: 225.
<http://www.ncbi.nlm.nih.gov/pubmed/18203940>
53. Regine, G., *et al.* Second-generation sonographic contrast agents in the evaluation of renal trauma. *Radiol Med*, 2007. 112: 581.
<http://www.ncbi.nlm.nih.gov/pubmed/17563847>
54. Valentino, M., *et al.* Contrast-enhanced US evaluation in patients with blunt abdominal trauma. *J Ultrasound*, 2010. 13: 22.
<http://www.ncbi.nlm.nih.gov/pubmed/23396012>
55. Mihalik, J.E., *et al.* The use of contrast-enhanced ultrasound for the evaluation of solid abdominal organ injury in patients with blunt abdominal trauma. *J Trauma Acute Care Surg*, 2012. 73: 1100.
<http://www.ncbi.nlm.nih.gov/pubmed/22832765>
56. Cagini, L., *et al.* Contrast enhanced ultrasound (CEUS) in blunt abdominal trauma. *Crit Ultrasound J*, 2013. 5 Suppl 1: S9.
<http://www.ncbi.nlm.nih.gov/pubmed/23902930>
57. Heller, M.T., *et al.* MDCT of renal trauma: correlation to AAST organ injury scale. *Clin Imaging*, 2014. 38: 410.
<http://www.ncbi.nlm.nih.gov/pubmed/24667041>
58. Huber-Wagner, S., *et al.* Effect of whole-body CT during trauma resuscitation on survival: a retrospective, multicentre study. *Lancet*, 2009. 373: 1455.
<http://www.ncbi.nlm.nih.gov/pubmed/19321199>
59. Alonso, R.C., *et al.* Kidney in danger: CT findings of blunt and penetrating renal trauma. *Radiographics*, 2009. 29: 2033.
<http://www.ncbi.nlm.nih.gov/pubmed/19926761>
60. Colling, K.P., *et al.* Computed tomography scans with intravenous contrast: low incidence of contrast-induced nephropathy in blunt trauma patients. *J Trauma Acute Care Surg*, 2014. 77: 226.
<https://www.ncbi.nlm.nih.gov/pubmed/25058246>
61. Fischer, W., *et al.* JOURNAL CLUB: Incidence of Urinary Leak and Diagnostic Yield of Excretory Phase CT in the Setting of Renal Trauma. *AJR Am J Roentgenol*, 2015. 204: 1168.
<http://www.ncbi.nlm.nih.gov/pubmed/26001225>
62. Morey, A.F., *et al.* Single shot intraoperative excretory urography for the immediate evaluation of renal trauma. *J Urol*, 1999. 161: 1088.
<http://www.ncbi.nlm.nih.gov/pubmed/10081844>
63. Ku, J.H., *et al.* Is there a role for magnetic resonance imaging in renal trauma? *Int J Urol*, 2001. 8: 261.
<http://www.ncbi.nlm.nih.gov/pubmed/11389740>
64. Leppaniemi, A., *et al.* MRI and CT in blunt renal trauma: an update. *Semin Ultrasound CT MR*, 1997. 18: 129.
<http://www.ncbi.nlm.nih.gov/pubmed/9163832>
65. Schmidlin, F.R., *et al.* [The conservative treatment of major kidney injuries]. *Ann Urol (Paris)*, 1997. 31: 246.
<http://www.ncbi.nlm.nih.gov/pubmed/9480627>
66. Holmes, J.F., *et al.* Rate of intra-abdominal injury after a normal abdominal computed tomographic scan in adults with blunt trauma. *Am J Emerg Med*, 2012. 30: 574.
<http://www.ncbi.nlm.nih.gov/pubmed/21641163>
67. Thall, E.H., *et al.* Conservative management of penetrating and blunt Type III renal injuries. *Br J Urol*, 1996. 77: 512.
<http://www.ncbi.nlm.nih.gov/pubmed/8777609>
68. Alsikafi, N.F., *et al.* Nonoperative management outcomes of isolated urinary extravasation following renal lacerations due to external trauma. *J Urol*, 2006. 176: 2494.
<http://www.ncbi.nlm.nih.gov/pubmed/17085140>

69. Buckley, J.C., *et al.* Selective management of isolated and nonisolated grade IV renal injuries. *J Urol*, 2006. 176: 2498.
<http://www.ncbi.nlm.nih.gov/pubmed/17085141>
70. Santucci, R.A., *et al.* Grade IV renal injuries: evaluation, treatment, and outcome. *World J Surg*, 2001. 25: 1565.
<http://www.ncbi.nlm.nih.gov/pubmed/11775193>
71. Altman, A.L., *et al.* Selective nonoperative management of blunt grade 5 renal injury. *J Urol*, 2000. 164: 27.
<http://www.ncbi.nlm.nih.gov/pubmed/10840417>
72. Moudouni, S.M., *et al.* Management of major blunt renal lacerations: is a nonoperative approach indicated? *Eur Urol*, 2001. 40: 409.
<http://www.ncbi.nlm.nih.gov/pubmed/11713395>
73. Husmann, D.A., *et al.* Attempted nonoperative management of blunt renal lacerations extending through the corticomedullary junction: the short-term and long-term sequelae. *J Urol*, 1990. 143: 682.
<http://www.ncbi.nlm.nih.gov/pubmed/2313792>
74. Elliott, S.P., *et al.* Renal arterial injuries: a single center analysis of management strategies and outcomes. *J Urol*, 2007. 178: 2451.
<http://www.ncbi.nlm.nih.gov/pubmed/17937955>
75. Jawas, A., *et al.* Management algorithm for complete blunt renal artery occlusion in multiple trauma patients: case series. *Int J Surg*, 2008. 6: 317.
<http://www.ncbi.nlm.nih.gov/pubmed/18590988>
76. Armenakas, N.A., *et al.* Indications for nonoperative management of renal stab wounds. *J Urol*, 1999. 161: 768.
<http://www.ncbi.nlm.nih.gov/pubmed/10022681>
77. Jansen, J.O., *et al.* Selective non-operative management of abdominal gunshot wounds: survey of practise. *Injury*, 2013. 44: 639.
<http://www.ncbi.nlm.nih.gov/pubmed/22341771>
78. Bernath, A.S., *et al.* Stab wounds of the kidney: conservative management in flank penetration. *J Urol*, 1983. 129: 468.
<http://www.ncbi.nlm.nih.gov/pubmed/6834529>
79. Wessells, H., *et al.* Criteria for nonoperative treatment of significant penetrating renal lacerations. *J Urol*, 1997. 157: 24.
<http://www.ncbi.nlm.nih.gov/pubmed/8976207>
80. Velmahos, G.C., *et al.* Selective management of renal gunshot wounds. *Br J Surg*, 1998. 85: 1121.
<http://www.ncbi.nlm.nih.gov/pubmed/9718011>
81. Baniel, J., *et al.* The management of penetrating trauma to the urinary tract. *J Am Coll Surg*, 1994. 178: 417.
<http://www.ncbi.nlm.nih.gov/pubmed/8149045>
82. DuBose, J., *et al.* Selective non-operative management of solid organ injury following abdominal gunshot wounds. *Injury*, 2007. 38: 1084.
<http://www.ncbi.nlm.nih.gov/pubmed/17544428>
83. Shefler, A., *et al.* [The role of nonoperative management of penetrating renal trauma]. *Harefuah*, 2007. 146: 345.
<http://www.ncbi.nlm.nih.gov/pubmed/17674549>
84. Hope, W.W., *et al.* Non-operative management in penetrating abdominal trauma: is it feasible at a Level II trauma center? *J Emerg Med*, 2012. 43: 190.
<http://www.ncbi.nlm.nih.gov/pubmed/22051843>
85. Lanchon, C., *et al.* High Grade Blunt Renal Trauma: Predictors of Surgery and Long-Term Outcomes of Conservative Management. A Prospective Single Center Study. *J Urol*, 2016. 195: 106.
<http://www.ncbi.nlm.nih.gov/pubmed/26254724>
86. Shoobridge, J.J., *et al.* A 9-year experience of renal injury at an Australian level 1 trauma centre. *BJU Int*, 2013. 112 Suppl 2: 53.
<http://www.ncbi.nlm.nih.gov/pubmed/23418742>
87. van der Wilden, G.M., *et al.* Successful nonoperative management of the most severe blunt renal injuries: a multicenter study of the research consortium of New England Centers for Trauma. *JAMA Surg*, 2013. 148: 924.
<http://www.ncbi.nlm.nih.gov/pubmed/23945834>

88. Charbit, J., *et al.* What are the specific computed tomography scan criteria that can predict or exclude the need for renal angioembolization after high-grade renal trauma in a conservative management strategy? *J Trauma*, 2011. 70: 1219.
<http://www.ncbi.nlm.nih.gov/pubmed/21610436>
89. Lin, W.C., *et al.* Computed tomographic imaging in determining the need of embolization for high-grade blunt renal injury. *J Trauma Acute Care Surg*, 2013. 74: 230.
<http://www.ncbi.nlm.nih.gov/pubmed/23271099>
90. Huber, J., *et al.* Selective transarterial embolization for posttraumatic renal hemorrhage: a second try is worthwhile. *J Urol*, 2011. 185: 1751.
<http://www.ncbi.nlm.nih.gov/pubmed/21420122>
91. Hotaling, J.M., *et al.* Analysis of diagnostic angiography and angioembolization in the acute management of renal trauma using a national data set. *J Urol*, 2011. 185: 1316.
<http://www.ncbi.nlm.nih.gov/pubmed/21334643>
92. Saour, M., *et al.* Effect of renal angioembolization on post-traumatic acute kidney injury after high-grade renal trauma: a comparative study of 52 consecutive cases. *Injury*, 2014. 45: 894.
<http://www.ncbi.nlm.nih.gov/pubmed/24456608>
93. Moolman, C., *et al.* Nonoperative management of penetrating kidney injuries: a prospective audit. *J Urol*, 2012. 188: 169.
<http://www.ncbi.nlm.nih.gov/pubmed/22591960>
94. Bjurlin, M.A., *et al.* Comparison of nonoperative management with renorrhaphy and nephrectomy in penetrating renal injuries. *J Trauma*, 2011. 71: 554.
<http://www.ncbi.nlm.nih.gov/pubmed/21610541>
95. Glass, A.S., *et al.* Selective angioembolization for traumatic renal injuries: a survey on clinician practice. *World J Urol*, 2014. 32: 821.
<http://www.ncbi.nlm.nih.gov/pubmed/24072011>
96. Husmann, D.A., *et al.* Major renal lacerations with a devitalized fragment following blunt abdominal trauma: a comparison between nonoperative (expectant) versus surgical management. *J Urol*, 1993. 150: 1774.
<http://www.ncbi.nlm.nih.gov/pubmed/24072011>
97. McAninch, J.W., *et al.* Renal reconstruction after injury. *J Urol*, 1991. 145: 932.
<http://www.ncbi.nlm.nih.gov/pubmed/2016804>
98. Hotaling, J.M., *et al.* A national study of trauma level designation and renal trauma outcomes. *J Urol*, 2012. 187: 536.
<http://www.ncbi.nlm.nih.gov/pubmed/22177171>
99. Broghammer, J.A., *et al.* Conservative management of renal trauma: a review. *Urology*, 2007. 70: 623.
<http://www.ncbi.nlm.nih.gov/pubmed/17991526>
100. Sartorelli, K.H., *et al.* Nonoperative management of hepatic, splenic, and renal injuries in adults with multiple injuries. *J Trauma*, 2000. 49: 56.
<http://www.ncbi.nlm.nih.gov/pubmed/10912858>
101. Toutouzas, K.G., *et al.* Nonoperative management of blunt renal trauma: a prospective study. *Am Surg*, 2002. 68: 1097.
<http://www.ncbi.nlm.nih.gov/pubmed/12516817>
102. Hammer, C.C., *et al.* Effect of an institutional policy of nonoperative treatment of grades I to IV renal injuries. *J Urol*, 2003. 169: 1751.
<http://www.ncbi.nlm.nih.gov/pubmed/12686825>
103. Robert, M., *et al.* Management of major blunt renal lacerations: surgical or nonoperative approach? *Eur Urol*, 1996. 30: 335.
<http://www.ncbi.nlm.nih.gov/pubmed/8931966>
104. Nash, P.A., *et al.* Nephrectomy for traumatic renal injuries. *J Urol*, 1995. 153: 609.
<http://www.ncbi.nlm.nih.gov/pubmed/7861494>
105. Gonzalez, R.P., *et al.* Surgical management of renal trauma: is vascular control necessary? *J Trauma*, 1999. 47: 1039.
<http://www.ncbi.nlm.nih.gov/pubmed/10608530>
106. Atala, A., *et al.* Preliminary vascular control for renal trauma. *Surg Gynecol Obstet*, 1991. 172: 386.
<http://www.ncbi.nlm.nih.gov/pubmed/2028374>
107. Chaabouni, M.N., *et al.* [Application of a peri-renal prosthesis (vicryl mesh) in the conservative treatment of multiple ruptured kidney fragments]. *Ann Urol (Paris)*, 1996. 30: 61.
<http://www.ncbi.nlm.nih.gov/pubmed/8767808>

108. Master, V.A., *et al.* Operative management of renal injuries: parenchymal and vascular. *Urol Clin North Am*, 2006. 33: 21.
<http://www.ncbi.nlm.nih.gov/pubmed/16488277>
109. Davis, K.A., *et al.* Predictors of the need for nephrectomy after renal trauma. *J Trauma*, 2006. 60: 164.
<http://www.ncbi.nlm.nih.gov/pubmed/16456451>
110. Wright, J.L., *et al.* Renal and extrarenal predictors of nephrectomy from the national trauma data bank. *J Urol*, 2006. 175: 970.
<http://www.ncbi.nlm.nih.gov/pubmed/16469594>
111. DiGiacomo, J.C., *et al.* The role of nephrectomy in the acutely injured. *Arch Surg*, 2001. 136: 1045.
<http://www.ncbi.nlm.nih.gov/pubmed/11529828>
112. Brandes, S.B., *et al.* Reconstructive surgery for trauma of the upper urinary tract. *Urol Clin North Am*, 1999. 26: 183.
<http://www.ncbi.nlm.nih.gov/pubmed/10086060>
113. McAninch, J.W., *et al.* [The surgical treatment of renal trauma]. *Vestn Khir Im I I Grek*, 1990. 145: 64.
<http://www.ncbi.nlm.nih.gov/pubmed/1966179>
114. Shekarriz, B., *et al.* The use of fibrin sealant in urology. *J Urol*, 2002. 167: 1218.
<http://www.ncbi.nlm.nih.gov/pubmed/11832701>
115. Knudson, M.M., *et al.* Outcome after major renovascular injuries: a Western trauma association multicenter report. *J Trauma*, 2000. 49: 1116.
<http://www.ncbi.nlm.nih.gov/pubmed/11130498>
116. Tillou, A., *et al.* Renal vascular injuries. *Surg Clin North Am*, 2001. 81: 1417.
<https://www.ncbi.nlm.nih.gov/pubmed/11766183>
117. Blankenship, J.C., *et al.* Importance of delayed imaging for blunt renal trauma. *World J Surg*, 2001. 25: 1561.
<https://www.ncbi.nlm.nih.gov/pubmed/11775192>
118. McGuire, J., *et al.* Predictors of outcome for blunt high grade renal injury treated with conservative intent. *J Urol*, 2011. 185: 187.
<https://www.ncbi.nlm.nih.gov/pubmed/21074795>
119. Wessells, H., *et al.* Preservation of renal function after reconstruction for trauma: quantitative assessment with radionuclide scintigraphy. *J Urol*, 1997. 157: 1583.
<https://www.ncbi.nlm.nih.gov/pubmed/9112481>
120. Tasian, G.E., *et al.* Evaluation of renal function after major renal injury: correlation with the American Association for the Surgery of Trauma Injury Scale. *J Urol*, 2010. 183: 196.
<https://www.ncbi.nlm.nih.gov/pubmed/19913819>
121. Fiard, G., *et al.* Long-term renal function assessment with dimercapto-succinic acid scintigraphy after conservative treatment of major renal trauma. *J Urol*, 2012. 187: 1306.
<https://www.ncbi.nlm.nih.gov/pubmed/22341289>
122. Dunfee, B.L., *et al.* Development of renal scars on CT after abdominal trauma: does grade of injury matter? *AJR Am J Roentgenol*, 2008. 190: 1174.
<https://www.ncbi.nlm.nih.gov/pubmed/18430828>
123. Heyns, C.F., *et al.* Increasing role of angiography and segmental artery embolization in the management of renal stab wounds. *J Urol*, 1992. 147: 1231.
<https://www.ncbi.nlm.nih.gov/pubmed/1569655>
124. Monstrey, S.J., *et al.* Renal trauma and hypertension. *J Trauma*, 1989. 29: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/2911106>
125. Lebech, A., *et al.* [Hypertension following blunt kidney injury]. *Ugeskr Laeger*, 1990. 152: 994.
<https://www.ncbi.nlm.nih.gov/pubmed/2183457>
126. Montgomery, R.C., *et al.* Posttraumatic renovascular hypertension after occult renal injury. *J Trauma*, 1998. 45: 106.
<https://www.ncbi.nlm.nih.gov/pubmed/9680021>
127. Haas, C.A., *et al.* Use of ureteral stents in the management of major renal trauma with urinary extravasation: is there a role? *J Endourol*, 1998. 12: 545.
<https://www.ncbi.nlm.nih.gov/pubmed/9895260>
128. Matthews, L.A., *et al.* Nonoperative treatment of major blunt renal lacerations with urinary extravasation. *J Urol*, 1997. 157: 2056.
<https://www.ncbi.nlm.nih.gov/pubmed/9146579>
129. Wang, K.T., *et al.* Late development of renal arteriovenous fistula following gunshot trauma--a case report. *Angiology*, 1998. 49: 415.
<https://www.ncbi.nlm.nih.gov/pubmed/9591535>

130. Salazar, G.M., *et al.* Evaluation and management of acute vascular trauma. *Tech Vasc Interv Radiol*, 2009. 12: 102.
<https://www.ncbi.nlm.nih.gov/pubmed/19853228>
131. Miller, D.C., *et al.* Successful angioembolization of renal artery pseudoaneurysms after blunt abdominal trauma. *Urology*, 2002. 59: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/11880095>
132. Harrington, T.G., *et al.* Renal colic following a gunshot wound to the abdomen: the birdshot calculus. *J Urol*, 1997. 157: 1351.
<https://www.ncbi.nlm.nih.gov/pubmed/9120940>
133. Heye, S., *et al.* Iatrogenic main renal artery injury: treatment by endovascular stent-graft placement. *Cardiovasc Intervent Radiol*, 2005. 28: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/15602634>
134. Maleux, G., *et al.* Transcatheter embolization of biopsy-related vascular injuries in renal allografts. Long-term technical, clinical and biochemical results. *Acta Radiol*, 2003. 44: 13.
<https://www.ncbi.nlm.nih.gov/pubmed/12630992>
135. Albani, J.M., *et al.* Renal artery pseudoaneurysm after partial nephrectomy: three case reports and a literature review. *Urology*, 2003. 62: 227.
<https://www.ncbi.nlm.nih.gov/pubmed/12893324>
136. Furness, P.N., *et al.* Protocol biopsy of the stable renal transplant: a multicenter study of methods and complication rates. *Transplantation*, 2003. 76: 969.
<https://www.ncbi.nlm.nih.gov/pubmed/14508363>
137. Barley, F.L., *et al.* Selective embolization of large symptomatic iatrogenic renal transplant arteriovenous fistula. *Cardiovasc Intervent Radiol*, 2006. 29: 1084.
<https://www.ncbi.nlm.nih.gov/pubmed/16794894>
138. Takahashi, M., *et al.* Early posttransplantation renal allograft perfusion failure due to dissection: diagnosis and interventional treatment. *AJR Am J Roentgenol*, 2003. 180: 759.
<https://www.ncbi.nlm.nih.gov/pubmed/12591692>
139. Bellman, G.C. Complications of endopyelotomy. *J Endourol*, 1996. 10: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/8728685>
140. Hinshaw, J.L., *et al.* Comparison of percutaneous and laparoscopic cryoablation for the treatment of solid renal masses. *AJR Am J Roentgenol*, 2008. 191: 1159.
<https://www.ncbi.nlm.nih.gov/pubmed/18806159>
141. Phadke, R.V., *et al.* Iatrogenic renal vascular injuries and their radiological management. *Clin Radiol*, 1997. 52: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/9043045>
142. Cohenpour, M., *et al.* Pseudoaneurysm of the renal artery following partial nephrectomy: imaging findings and coil embolization. *Clin Radiol*, 2007. 62: 1104.
<https://www.ncbi.nlm.nih.gov/pubmed/17920871>
143. Loffroy, R., *et al.* Management of post-biopsy renal allograft arteriovenous fistulas with selective arterial embolization: immediate and long-term outcomes. *Clin Radiol*, 2008. 63: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/18455557>
144. Ben Meir, D., *et al.* Intrarenal foreign body presenting as a solid tumor. *Urology*, 2003. 61: 1035.
<https://www.ncbi.nlm.nih.gov/pubmed/12736036>
145. Nakada, S.Y., *et al.* Ureteropelvic junction obstruction. Retrograde endopyelotomy. *Urol Clin North Am*, 2000. 27: 677.
<https://www.ncbi.nlm.nih.gov/pubmed/11098766>
146. Jones, C.D., *et al.* Computed tomographic evaluation and guided correction of malpositioned nephrostomy catheters. *Abdom Imaging*, 1999. 24: 422.
<https://www.ncbi.nlm.nih.gov/pubmed/10390572>
147. Silberzweig, J.E., *et al.* Percutaneous renal biopsy complicated by renal capsular artery pseudoaneurysm. *Am J Kidney Dis*, 1998. 31: 533.
<https://www.ncbi.nlm.nih.gov/pubmed/9506693>
148. Gupta, M., *et al.* Massive hemorrhage from renal vein injury during percutaneous renal surgery: endourological management. *J Urol*, 1997. 157: 795.
<https://www.ncbi.nlm.nih.gov/pubmed/9072568>
149. El-Nahas, A.R., *et al.* Post-percutaneous nephrolithotomy extensive hemorrhage: a study of risk factors. *J Urol*, 2007. 177: 576.
<https://www.ncbi.nlm.nih.gov/pubmed/17222636>

150. El-Nahas, A.R., *et al.* Functional and morphological effects of postpercutaneous nephrolithotomy superselective renal angiographic embolization. *Urology*, 2008. 71: 408.
<https://www.ncbi.nlm.nih.gov/pubmed/18342174>
151. Ghai, B., *et al.* Massive intraabdominal extravasation of fluid: a life threatening complication following percutaneous nephrolithotomy. *Int Urol Nephrol*, 2003. 35: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/15160530>
152. Oderich, G.S., *et al.* Iatrogenic operative injuries of abdominal and pelvic veins: a potentially lethal complication. *J Vasc Surg*, 2004. 39: 931.
<https://www.ncbi.nlm.nih.gov/pubmed/15111840>
153. Taneja, M., *et al.* Renal vascular injuries following nephron-sparing surgery and their endovascular management. *Singapore Med J*, 2008. 49: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/18204772>
154. Inci, K., *et al.* Renal artery pseudoaneurysm: complication of minimally invasive kidney surgery. *J Endourol*, 2010. 24: 149.
<https://www.ncbi.nlm.nih.gov/pubmed/19954351>
155. Perini, S., *et al.* Transcatheter embolization of biopsy-related vascular injury in the transplant kidney: immediate and long-term outcome. *J Vasc Interv Radiol*, 1998. 9: 1011.
<https://www.ncbi.nlm.nih.gov/pubmed/9840051>
156. Nakatani, T., *et al.* Renal allograft arteriovenous fistula and large pseudoaneurysm. *Clin Transplant*, 2003. 17: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/12588315>
157. Breyer, B.N., *et al.* Minimally invasive endovascular techniques to treat acute renal hemorrhage. *J Urol*, 2008. 179: 2248.
<https://www.ncbi.nlm.nih.gov/pubmed/18423679>
158. Wang, M.Q., *et al.* [Treatment of acquired arteriovenous fistulas with interventional minimally invasive techniques]. *Zhonghua Wai Ke Za Zhi*, 2004. 42: 687.
<https://www.ncbi.nlm.nih.gov/pubmed/15329261>
159. Morris, C.S., *et al.* Nonsurgical treatment of acute iatrogenic renal artery injuries occurring after renal artery angioplasty and stenting. *AJR Am J Roentgenol*, 2001. 177: 1353.
<https://www.ncbi.nlm.nih.gov/pubmed/11717082>
160. Elliott, S.P., *et al.* Ureteral injuries: external and iatrogenic. *Urol Clin North Am*, 2006. 33: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/16488280>
161. McGeady, J.B., *et al.* Current epidemiology of genitourinary trauma. *Urol Clin North Am*, 2013. 40: 323.
<https://www.ncbi.nlm.nih.gov/pubmed/23905930>
162. Siram, S.M., *et al.* Ureteral trauma: patterns and mechanisms of injury of an uncommon condition. *Am J Surg*, 2010. 199: 566.
<https://www.ncbi.nlm.nih.gov/pubmed/20359576>
163. Serkin, F.B., *et al.* Combat urologic trauma in US military overseas contingency operations. *J Trauma*, 2010. 69 Suppl 1: S175.
<https://www.ncbi.nlm.nih.gov/pubmed/20622614>
164. Brandes, S., *et al.* Diagnosis and management of ureteric injury: an evidence-based analysis. *BJU Int*, 2004. 94: 277.
<https://www.ncbi.nlm.nih.gov/pubmed/15291852>
165. Chou, M.T., *et al.* Prophylactic ureteral catheterization in gynecologic surgery: a 12-year randomized trial in a community hospital. *Int Urogynecol J Pelvic Floor Dysfunct*, 2009. 20: 689.
<https://www.ncbi.nlm.nih.gov/pubmed/19165412>
166. Delacroix, S.E., Jr., *et al.* Urinary tract injuries: recognition and management. *Clin Colon Rectal Surg*, 2010. 23: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/21629628>
167. Visco, A.G., *et al.* Cost-effectiveness of universal cystoscopy to identify ureteral injury at hysterectomy. *Obstet Gynecol*, 2001. 97: 685.
<https://www.ncbi.nlm.nih.gov/pubmed/11339916>
168. Halabi, W.J., *et al.* Ureteral injuries in colorectal surgery: an analysis of trends, outcomes, and risk factors over a 10-year period in the United States. *Dis Colon Rectum*, 2014. 57: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/24401879>
169. Johnson, D.B., *et al.* Complications of ureteroscopy. *Urol Clin North Am*, 2004. 31: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/15040412>

170. Schimpf, M.O., *et al.* Universal ureteral stent placement at hysterectomy to identify ureteral injury: a decision analysis. *BJOG*, 2008. 115: 1151.
<https://www.ncbi.nlm.nih.gov/pubmed/18518875>
171. Gilmour, D.T., *et al.* Rates of urinary tract injury from gynecologic surgery and the role of intraoperative cystoscopy. *Obstet Gynecol*, 2006. 107: 1366.
<https://www.ncbi.nlm.nih.gov/pubmed/16738165>
172. Wu, H.H., *et al.* The detection of ureteral injuries after hysterectomy. *J Minim Invasive Gynecol*, 2006. 13: 403.
<https://www.ncbi.nlm.nih.gov/pubmed/16962522>
173. Pokala, N., *et al.* A randomized controlled trial comparing simultaneous intra-operative vs sequential prophylactic ureteric catheter insertion in re-operative and complicated colorectal surgery. *Int J Colorectal Dis*, 2007. 22: 683.
<https://www.ncbi.nlm.nih.gov/pubmed/17031654>
174. Jhaveri, J.K., *et al.* Ureteral injuries sustained during robot-assisted radical prostatectomy. *J Endourol*, 2014. 28: 318.
<https://www.ncbi.nlm.nih.gov/pubmed/24147874>
175. Kunkle, D.A., *et al.* Delayed diagnosis of traumatic ureteral injuries. *J Urol*, 2006. 176: 2503.
<https://www.ncbi.nlm.nih.gov/pubmed/17085143>
176. Parpala-Sparman, T., *et al.* Increasing numbers of ureteric injuries after the introduction of laparoscopic surgery. *Scand J Urol Nephrol*, 2008. 42: 422.
<https://www.ncbi.nlm.nih.gov/pubmed/18609278>
177. Medina, D., *et al.* Ureteral trauma: preoperative studies neither predict injury nor prevent missed injuries. *J Am Coll Surg*, 1998. 186: 641.
<https://www.ncbi.nlm.nih.gov/pubmed/9632150>
178. Lucarelli, G., *et al.* Delayed relief of ureteral obstruction is implicated in the long-term development of renal damage and arterial hypertension in patients with unilateral ureteral injury. *J Urol*, 2013. 189: 960.
<https://www.ncbi.nlm.nih.gov/pubmed/23017525>
179. Speicher, P.J., *et al.* Ureteral stenting in laparoscopic colorectal surgery. *J Surg Res*, 2014. 190: 98.
<https://www.ncbi.nlm.nih.gov/pubmed/24656474>
180. Smith, T.G., 3rd, *et al.* Damage control maneuvers for urologic trauma. *Urol Clin North Am*, 2013. 40: 343.
<https://www.ncbi.nlm.nih.gov/pubmed/23905932>
181. Koukouras, D., *et al.* Percutaneous minimally invasive management of iatrogenic ureteral injuries. *J Endourol*, 2010. 24: 1921.
<https://www.ncbi.nlm.nih.gov/pubmed/20964484>
182. El Abd, A.S., *et al.* Immediate and late management of iatrogenic ureteric injuries: 28 years of experience. *Arab J Urol*, 2015. 13: 250.
<https://www.ncbi.nlm.nih.gov/pubmed/26609443>
183. Png, J.C., *et al.* Principles of ureteric reconstruction. *Curr Opin Urol*, 2000. 10: 207.
<https://www.ncbi.nlm.nih.gov/pubmed/10858898>
184. Burks, F.N., *et al.* Management of iatrogenic ureteral injury. *Ther Adv Urol*, 2014. 6: 115.
<https://www.ncbi.nlm.nih.gov/pubmed/24883109>
185. Wenske, S., *et al.* Outcomes of distal ureteral reconstruction through reimplantation with psoas hitch, Boari flap, or ureteroneocystostomy for benign or malignant ureteral obstruction or injury. *Urology*, 2013. 82: 231.
<https://www.ncbi.nlm.nih.gov/pubmed/23642933>
186. Chung, B.I., *et al.* The use of bowel for ureteral replacement for complex ureteral reconstruction: long-term results. *J Urol*, 2006. 175: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/16406903>
187. Armatys, S.A., *et al.* Use of ileum as ureteral replacement in urological reconstruction. *J Urol*, 2009. 181: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/19013597>
188. Meng, M.V., *et al.* Expanded experience with laparoscopic nephrectomy and autotransplantation for severe ureteral injury. *J Urol*, 2003. 169: 1363.
<https://www.ncbi.nlm.nih.gov/pubmed/12629362>
189. Pereira, B.M., *et al.* Bladder injuries after external trauma: 20 years experience report in a population-based cross-sectional view. *World J Urol*, 2013. 31: 913.
<https://www.ncbi.nlm.nih.gov/pubmed/22544337>

190. Figler, B.D., *et al.* Multi-disciplinary update on pelvic fracture associated bladder and urethral injuries. *Injury*, 2012. 43: 1242.
<https://www.ncbi.nlm.nih.gov/pubmed/22592152>
191. Wirth, G.J., *et al.* Advances in the management of blunt traumatic bladder rupture: experience with 36 cases. *BJU Int*, 2010. 106: 1344.
<https://www.ncbi.nlm.nih.gov/pubmed/20438556>
192. Deibert, C.M., *et al.* The association between operative repair of bladder injury and improved survival: results from the National Trauma Data Bank. *J Urol*, 2011. 186: 151.
<https://www.ncbi.nlm.nih.gov/pubmed/21575961>
193. Matlock, K.A., *et al.* Blunt traumatic bladder rupture: a 10-year perspective. *Am Surg*, 2013. 79: 589.
<https://www.ncbi.nlm.nih.gov/pubmed/23711268>
194. Cinman, N.M., *et al.* Gunshot wounds to the lower urinary tract: a single-institution experience. *J Trauma Acute Care Surg*, 2013. 74: 725.
<https://www.ncbi.nlm.nih.gov/pubmed/23425728>
195. Al-Azzawi, I.S., *et al.* Lower genitourinary trauma in modern warfare: the experience from civil violence in Iraq. *Injury*, 2014. 45: 885.
<https://www.ncbi.nlm.nih.gov/pubmed/24485550>
196. Williams, M., *et al.* Management of combat-related urological trauma in the modern era. *Nat Rev Urol*, 2013. 10: 504.
<https://www.ncbi.nlm.nih.gov/pubmed/23877722>
197. Cordon, B.H., *et al.* Iatrogenic nonendoscopic bladder injuries over 24 years: 127 cases at a single institution. *Urology*, 2014. 84: 222.
<https://www.ncbi.nlm.nih.gov/pubmed/24857278>
198. Tarney, C.M. Bladder Injury During Cesarean Delivery. *Curr Womens Health Rev*, 2013. 9: 70.
<https://www.ncbi.nlm.nih.gov/pubmed/24876830>
199. Shazly, S.A., *et al.* Robotic radical hysterectomy in early stage cervical cancer: A systematic review and meta-analysis. *Gynecol Oncol*, 2015. 138: 457.
<https://www.ncbi.nlm.nih.gov/pubmed/26056752>
200. Brummer, T.H., *et al.* FINHYST, a prospective study of 5279 hysterectomies: complications and their risk factors. *Hum Reprod*, 2011. 26: 1741.
<https://www.ncbi.nlm.nih.gov/pubmed/21540244>
201. Sawkar, H.P., *et al.* Frequency of lower urinary tract injury after gastrointestinal surgery in the nationwide inpatient sample database. *Am Surg*, 2014. 80: 1216.
<https://www.ncbi.nlm.nih.gov/pubmed/25513920>
202. Honore, C., *et al.* HIPEC for peritoneal carcinomatosis: does an associated urologic procedure increase morbidity? *Ann Surg Oncol*, 2012. 19: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/21638092>
203. Kockerling, F., *et al.* TEP versus TAPP: comparison of the perioperative outcome in 17,587 patients with a primary unilateral inguinal hernia. *Surg Endosc*, 2015. 29: 3750.
<https://www.ncbi.nlm.nih.gov/pubmed/25805239>
204. Welk, B.K., *et al.* Are male slings for post-prostatectomy incontinence a valid option? *Curr Opin Urol*, 2010. 20: 465.
<https://www.ncbi.nlm.nih.gov/pubmed/20838219>
205. Maher, C.F., *et al.* Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: a randomized trial. *Am J Obstet Gynecol*, 2011. 204: 360 e1.
<https://www.ncbi.nlm.nih.gov/pubmed/21306698>
206. Novara, G., *et al.* Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. *Eur Urol*, 2010. 58: 218.
<https://www.ncbi.nlm.nih.gov/pubmed/20434257>
207. Ogah, J., *et al.* Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. *Neurourol Urodyn*, 2011. 30: 284.
<https://www.ncbi.nlm.nih.gov/pubmed/21412819>
208. Maher, C., *et al.* Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. *Cochrane Database Syst Rev*, 2016. 2: CD012079.
<https://www.ncbi.nlm.nih.gov/pubmed/26858090>
209. Balbay, M.D., *et al.* The actual incidence of bladder perforation following transurethral bladder surgery. *J Urol*, 2005. 174: 2260.
<https://www.ncbi.nlm.nih.gov/pubmed/16280794>

210. Nieder, A.M., *et al.* Transurethral bladder tumor resection: intraoperative and postoperative complications in a residency setting. *J Urol*, 2005. 174: 2307.
<https://www.ncbi.nlm.nih.gov/pubmed/16280830>
211. Golan, S., *et al.* Transurethral resection of bladder tumour complicated by perforation requiring open surgical repair - clinical characteristics and oncological outcomes. *BJU Int*, 2011. 107: 1065.
<https://www.ncbi.nlm.nih.gov/pubmed/20860654>
212. El Hayek, O.R., *et al.* Evaluation of the incidence of bladder perforation after transurethral bladder tumor resection in a residency setting. *J Endourol*, 2009. 23: 1183.
<https://www.ncbi.nlm.nih.gov/pubmed/19530900>
213. Sugihara, T., *et al.* Comparison of perioperative outcomes including severe bladder injury between monopolar and bipolar transurethral resection of bladder tumors: a population based comparison. *J Urol*, 2014. 192: 1355.
<https://www.ncbi.nlm.nih.gov/pubmed/24893311>
214. Venkatramani, V., *et al.* Monopolar versus bipolar transurethral resection of bladder tumors: a single center, parallel arm, randomized, controlled trial. *J Urol*, 2014. 191: 1703.
<https://www.ncbi.nlm.nih.gov/pubmed/24333244>
215. Collado, A., *et al.* Early complications of endoscopic treatment for superficial bladder tumors. *J Urol*, 2000. 164: 1529.
<https://www.ncbi.nlm.nih.gov/pubmed/11025697>
216. Rafique, M. Intravesical foreign bodies: review and current management strategies. *Urol J*, 2008. 5: 223.
<https://www.ncbi.nlm.nih.gov/pubmed/19101894>
217. Barber, M.D. Surgical techniques for removing problematic mesh. *Clin Obstet Gynecol*, 2013. 56: 289.
<https://www.ncbi.nlm.nih.gov/pubmed/23563870>
218. Pereira, B.M., *et al.* Penetrating bladder trauma: a high risk factor for associated rectal injury. *Adv Urol*, 2014. 2014: 386280.
<https://www.ncbi.nlm.nih.gov/pubmed/24527030>
219. Clarke-Pearson, D.L., *et al.* Complications of hysterectomy. *Obstet Gynecol*, 2013. 121: 654.
<https://www.ncbi.nlm.nih.gov/pubmed/23635631>
220. Manikandan, R., *et al.* Percutaneous peritoneal drainage for intraperitoneal bladder perforations during transurethral resection of bladder tumors. *J Endourol*, 2003. 17: 945.
<https://www.ncbi.nlm.nih.gov/pubmed/14744369>
221. Patel, B.N., *et al.* Imaging of iatrogenic complications of the urinary tract: kidneys, ureters, and bladder. *Radiol Clin North Am*, 2014. 52: 1101.
<https://www.ncbi.nlm.nih.gov/pubmed/25173661>
222. Lehnert, B.E., *et al.* Lower male genitourinary trauma: a pictorial review. *Emerg Radiol*, 2014. 21: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/24052083>
223. Quagliano, P.V., *et al.* Diagnosis of blunt bladder injury: A prospective comparative study of computed tomography cystography and conventional retrograde cystography. *J Trauma*, 2006. 61: 410.
<https://www.ncbi.nlm.nih.gov/pubmed/16917459>
224. Alperin, M., *et al.* Conservative management of postoperatively diagnosed cystotomy. *Urology*, 2009. 73: 1163 e17.
<https://www.ncbi.nlm.nih.gov/pubmed/18514295>
225. Teeluckdharry, B., *et al.* Urinary Tract Injury at Benign Gynecologic Surgery and the Role of Cystoscopy: A Systematic Review and Meta-analysis. *Obstet Gynecol*, 2015. 126: 1161.
<https://www.ncbi.nlm.nih.gov/pubmed/26551173>
226. Stember, D.S., *et al.* Outcomes of abdominal wall reservoir placement in inflatable penile prosthesis implantation: a safe and efficacious alternative to the space of Retzius. *J Sex Med*, 2014. 11: 605.
<https://www.ncbi.nlm.nih.gov/pubmed/24286533>
227. Oh, J.S., *et al.* Effectiveness of the combat pelvic protection system in the prevention of genital and urinary tract injuries: An observational study. *J Trauma Acute Care Surg*, 2015. 79: S193.
<https://www.ncbi.nlm.nih.gov/pubmed/26406430>
228. Pansadoro, A., *et al.* Conservative treatment of intraperitoneal bladder perforation during transurethral resection of bladder tumor. *Urology*, 2002. 60: 682.
<https://www.ncbi.nlm.nih.gov/pubmed/12385934>

229. Navsaria, P.H., *et al.* Selective nonoperative management in 1106 patients with abdominal gunshot wounds: conclusions on safety, efficacy, and the role of selective CT imaging in a prospective single-center study. *Ann Surg*, 2015. 261: 760.
<https://www.ncbi.nlm.nih.gov/pubmed/25185470>
230. Inaba, K., *et al.* Selective nonoperative management of torso gunshot wounds: when is it safe to discharge? *J Trauma*, 2010. 68: 1301.
<https://www.ncbi.nlm.nih.gov/pubmed/22341771>
231. Lee, J.S., *et al.* Urologic complications following obstetric and gynecologic surgery. *Korean J Urol*, 2012. 53: 795.
<https://www.ncbi.nlm.nih.gov/pubmed/23185673>
232. Traxer, O., *et al.* Technique and complications of transurethral surgery for bladder tumours. *BJU Int*, 2004. 94: 492.
<https://www.ncbi.nlm.nih.gov/pubmed/15329099>
233. Stav, K., *et al.* Risk factors for trocar injury to the bladder during mid urethral sling procedures. *J Urol*, 2009. 182: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/19450824>
234. Inaba, K., *et al.* Prospective evaluation of the utility of routine postoperative cystogram after traumatic bladder injury. *J Trauma Acute Care Surg*, 2013. 75: 1019.
<https://www.ncbi.nlm.nih.gov/pubmed/24256676>
235. Frenkl, T.L., *et al.* Management of iatrogenic foreign bodies of the bladder and urethra following pelvic floor surgery. *Neurourol Urodyn*, 2008. 27: 491.
<https://www.ncbi.nlm.nih.gov/pubmed/18537142>
236. Mundy, A.R., *et al.* Urethral trauma. Part I: introduction, history, anatomy, pathology, assessment and emergency management. *BJU Int*, 2011. 108: 310.
<https://www.ncbi.nlm.nih.gov/pubmed/19874306>
237. Kashefi, C., *et al.* Incidence and prevention of iatrogenic urethral injuries. *J Urol*, 2008. 179: 2254.
<https://www.ncbi.nlm.nih.gov/pubmed/18423712>
238. Fenton, A.S., *et al.* Anterior urethral strictures: etiology and characteristics. *Urology*, 2005. 65: 1055.
<https://www.ncbi.nlm.nih.gov/pubmed/15913734>
239. Buddha, S. Complication of urethral catheterisation. *Lancet*, 2005. 365: 909.
<https://www.ncbi.nlm.nih.gov/pubmed/15752537>
240. Hammarsten, J., *et al.* Suprapubic catheter following transurethral resection of the prostate: a way to decrease the number of urethral strictures and improve the outcome of operations. *J Urol*, 1992. 147: 648.
<https://www.ncbi.nlm.nih.gov/pubmed/1538447>
241. Katz, G., *et al.* Prevention of urethral strictures following coronary artery bypass graft surgery. *Urology*, 1992. 39: 433.
<https://www.ncbi.nlm.nih.gov/pubmed/1580032>
242. Thomas, A.Z., *et al.* Avoidable iatrogenic complications of urethral catheterization and inadequate intern training in a tertiary-care teaching hospital. *BJU Int*, 2009. 104: 1109.
<https://www.ncbi.nlm.nih.gov/pubmed/19338562>
243. Vicente, J., *et al.* Value of electrical dispersion as a cause of urethral stenosis after endoscopic surgery. *Eur Urol*, 1992. 21: 280.
<https://www.ncbi.nlm.nih.gov/pubmed/1459149>
244. Komura, K., *et al.* Incidence of urethral stricture after bipolar transurethral resection of the prostate using TURis: results from a randomised trial. *BJU Int*, 2015. 115: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/24909399>
245. Stucki, P., *et al.* Bipolar versus monopolar transurethral resection of the prostate: a prospective randomized trial focusing on bleeding complications. *J Urol*, 2015. 193: 1371.
<https://www.ncbi.nlm.nih.gov/pubmed/25464004>
246. Hammarsten, J., *et al.* Urethral strictures following transurethral resection of the prostate. The role of the catheter. *Br J Urol*, 1989. 63: 397.
<https://www.ncbi.nlm.nih.gov/pubmed/2713622>
247. Rassweiler, J., *et al.* Complications of transurethral resection of the prostate (TURP)--incidence, management, and prevention. *Eur Urol*, 2006. 50: 969.
<https://www.ncbi.nlm.nih.gov/pubmed/16469429>
248. Eltabey, M.A., *et al.* Holmium laser enucleation versus transurethral resection of the prostate. *Can J Urol*, 2010. 17: 5447.
<https://www.ncbi.nlm.nih.gov/pubmed/21172109>

249. Elliott, S.P., *et al.* Incidence of urethral stricture after primary treatment for prostate cancer: data From CaPSURE. *J Urol*, 2007. 178: 529.
<https://www.ncbi.nlm.nih.gov/pubmed/17570425>
250. Park, R., *et al.* Anastomotic strictures following radical prostatectomy: insights into incidence, effectiveness of intervention, effect on continence, and factors predisposing to occurrence. *Urology*, 2001. 57: 742.
<https://www.ncbi.nlm.nih.gov/pubmed/11306394>
251. Autorino, R., *et al.* Perioperative Outcomes of Robotic and Laparoscopic Simple Prostatectomy: A European-American Multi-institutional Analysis. *Eur Urol*, 2015. 68: 86.
<https://www.ncbi.nlm.nih.gov/pubmed/25484140>
252. Msezane, L.P., *et al.* Bladder neck contracture after robot-assisted laparoscopic radical prostatectomy: evaluation of incidence and risk factors and impact on urinary function. *J Endourol*, 2008. 22: 97.
<https://www.ncbi.nlm.nih.gov/pubmed/18326071>
253. Ficarra, V., *et al.* Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. *Eur Urol*, 2009. 55: 1037.
<https://www.ncbi.nlm.nih.gov/pubmed/19185977>
254. Chrouser, K.L., *et al.* Urinary fistulas following external radiation or permanent brachytherapy for the treatment of prostate cancer. *J Urol*, 2005. 173: 1953.
<https://www.ncbi.nlm.nih.gov/pubmed/15879789>
255. Marguet, C., *et al.* Rectourethral fistula after combination radiotherapy for prostate cancer. *Urology*, 2007. 69: 898.
<https://www.ncbi.nlm.nih.gov/pubmed/17482930>
256. Gomez-Iturriaga Pina, A., *et al.* Median 5 year follow-up of 125iodine brachytherapy as monotherapy in men aged <or=55 years with favorable prostate cancer. *Urology*, 2010. 75: 1412.
<https://www.ncbi.nlm.nih.gov/pubmed/20035986>
257. Fonteyne, V., *et al.* Urinary toxicity after high dose intensity modulated radiotherapy as primary therapy for prostate cancer. *Radiother Oncol*, 2009. 92: 42.
<https://www.ncbi.nlm.nih.gov/pubmed/19356817>
258. Shelley, M., *et al.* Cryotherapy for localised prostate cancer. *Cochrane Database Syst Rev*, 2007: CD005010.
<https://www.ncbi.nlm.nih.gov/pubmed/17636783>
259. Polat, O., *et al.* Iatrogenic injuries to ureter, bladder and urethra during abdominal and pelvic operations. *Int Urol Nephrol*, 1997. 29: 13.
<https://www.ncbi.nlm.nih.gov/pubmed/9203032>
260. Hautmann, R.E., *et al.* 25 years of experience with 1,000 neobladders: long-term complications. *J Urol*, 2011. 185: 2207.
<https://www.ncbi.nlm.nih.gov/pubmed/21497841>
261. Chapple, C., *et al.* Consensus statement on urethral trauma. *BJU Int*, 2004. 93: 1195.
<https://www.ncbi.nlm.nih.gov/pubmed/15180604>
262. Brandes, S. Initial management of anterior and posterior urethral injuries. *Urol Clin North Am*, 2006. 33: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/16488283>
263. Park, S., *et al.* Straddle injuries to the bulbar urethra: management and outcomes in 78 patients. *J Urol*, 2004. 171: 722.
<https://www.ncbi.nlm.nih.gov/pubmed/14713796>
264. Elgammal, M.A. Straddle injuries to the bulbar urethra: management and outcome in 53 patients. *Int Braz J Urol*, 2009. 35: 450.
<https://www.ncbi.nlm.nih.gov/pubmed/19719861>
265. Kommu, S.S., *et al.* Patterns of urethral injury and immediate management. *Curr Opin Urol*, 2007. 17: 383.
<https://www.ncbi.nlm.nih.gov/pubmed/17921771>
266. Rosenstein, D.I., *et al.* Diagnosis and classification of urethral injuries. *Urol Clin North Am*, 2006. 33: 73.
<https://www.ncbi.nlm.nih.gov/pubmed/16488282>
267. Phonsombat, S., *et al.* Penetrating external genital trauma: a 30-year single institution experience. *J Urol*, 2008. 180: 192.
<https://www.ncbi.nlm.nih.gov/pubmed/18499189>

268. Simhan, J., *et al.* Gunshot wounds to the scrotum: a large single-institutional 20-year experience. *BJU Int*, 2012. 109: 1704.
<https://www.ncbi.nlm.nih.gov/pubmed/21992688>
269. Kunkle, D.A., *et al.* Evaluation and management of gunshot wounds of the penis: 20-year experience at an urban trauma center. *J Trauma*, 2008. 64: 1038.
<https://www.ncbi.nlm.nih.gov/pubmed/18404072>
270. Bjurlin, M.A., *et al.* Clinical characteristics and surgical outcomes of penetrating external genital injuries. *J Trauma Acute Care Surg*, 2013. 74: 839.
<https://www.ncbi.nlm.nih.gov/pubmed/23425745>
271. Amit, A., *et al.* Penile fracture and associated urethral injury: Experience at a tertiary care hospital. *Can Urol Assoc J*, 2013. 7: E168.
<https://www.ncbi.nlm.nih.gov/pubmed/23589751>
272. Lumen, N., *et al.* Etiology of urethral stricture disease in the 21st century. *J Urol*, 2009. 182: 983.
<https://www.ncbi.nlm.nih.gov/pubmed/19616805>
273. Palminteri, E., *et al.* Contemporary urethral stricture characteristics in the developed world. *Urology*, 2013. 81: 191.
<https://www.ncbi.nlm.nih.gov/pubmed/23153951>
274. Basta, A.M., *et al.* Predicting urethral injury from pelvic fracture patterns in male patients with blunt trauma. *J Urol*, 2007. 177: 571.
<https://www.ncbi.nlm.nih.gov/pubmed/17222635>
275. Barbagli, G., *et al.* The spectrum of pelvic fracture urethral injuries and posterior urethroplasty in an Italian high-volume centre, from 1980 to 2013. *Arab J Urol*, 2015. 13: 32.
<https://www.ncbi.nlm.nih.gov/pubmed/26019976>
276. Koraitim, M.M., *et al.* Risk factors and mechanism of urethral injury in pelvic fractures. *Br J Urol*, 1996. 77: 876.
<https://www.ncbi.nlm.nih.gov/pubmed/8705225>
277. Mundy, A.R., *et al.* Pelvic fracture-related injuries of the bladder neck and prostate: their nature, cause and management. *BJU Int*, 2010. 105: 1302.
<https://www.ncbi.nlm.nih.gov/pubmed/19874306>
278. Tausch, T.J., *et al.* Gunshot wound injuries of the prostate and posterior urethra: reconstructive armamentarium. *J Urol*, 2007. 178: 1346.
<https://www.ncbi.nlm.nih.gov/pubmed/17706720>
279. Koraitim, M.M. Predictors of erectile dysfunction post pelvic fracture urethral injuries: a multivariate analysis. *Urology*, 2013. 81: 1081.
<https://www.ncbi.nlm.nih.gov/pubmed/23465164>
280. Feng, C., *et al.* Risk factors for erectile dysfunction in patients with urethral strictures secondary to blunt trauma. *J Sex Med*, 2008. 5: 2656.
<https://www.ncbi.nlm.nih.gov/pubmed/18564154>
281. Metzke, M., *et al.* Male sexual dysfunction after pelvic fracture. *J Trauma*, 2007. 63: 394.
<https://www.ncbi.nlm.nih.gov/pubmed/17693842>
282. Bertrand, L.A., *et al.* Lower urinary tract pain and anterior urethral stricture disease: prevalence and effects of urethral reconstruction. *J Urol*, 2015. 193: 184.
<https://www.ncbi.nlm.nih.gov/pubmed/25046621>
283. Koraitim, M.M., *et al.* Role of magnetic resonance imaging in assessment of posterior urethral distraction defects. *Urology*, 2007. 70: 403.
<https://www.ncbi.nlm.nih.gov/pubmed/17905082>
284. Mundy, A.R., *et al.* Urethral trauma. Part II: Types of injury and their management. *BJU Int*, 2011. 108: 630.
<https://www.ncbi.nlm.nih.gov/pubmed/21854524>
285. Koraitim, M.M. Pelvic fracture urethral injuries: the unresolved controversy. *J Urol*, 1999. 161: 1433.
<https://www.ncbi.nlm.nih.gov/pubmed/10210368>
286. Hadjizacharia, P., *et al.* Evaluation of immediate endoscopic realignment as a treatment modality for traumatic urethral injuries. *J Trauma*, 2008. 64: 1443.
<https://www.ncbi.nlm.nih.gov/pubmed/18545107>
287. Rieder, J., *et al.* Review of intentionally self-inflicted, accidental and iatrogenic foreign objects in the genitourinary tract. *Urol Int*, 2010. 84: 471.
<https://www.ncbi.nlm.nih.gov/pubmed/20224259>
288. Kielb, S.J., *et al.* Evaluation and management of traumatic posterior urethral disruption with flexible cystourethroscopy. *J Trauma*, 2001. 50: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/11253761>

289. Mazaris, E.M., *et al.* Penile fractures: immediate surgical approach with a midline ventral incision. *BJU Int*, 2009. 104: 520.
<https://www.ncbi.nlm.nih.gov/pubmed/19239439>
290. Kamdar, C., *et al.* Penile fracture: preoperative evaluation and surgical technique for optimal patient outcome. *BJU Int*, 2008. 102: 1640.
<https://www.ncbi.nlm.nih.gov/pubmed/18710448>
291. Goonesinghe, S.K., *et al.* Flexible cystourethroscopy in the follow-up of posturethroplasty patients and characterisation of recurrences. *Eur Urol*, 2015. 68: 523.
<https://www.ncbi.nlm.nih.gov/pubmed/25913391>
292. Mouraviev, V.B., *et al.* The treatment of posterior urethral disruption associated with pelvic fractures: comparative experience of early realignment versus delayed urethroplasty. *J Urol*, 2005. 173: 873.
<https://www.ncbi.nlm.nih.gov/pubmed/15711301>
293. Derouiche, A., *et al.* Management of penile fractures complicated by urethral rupture. *Int J Impot Res*, 2008. 20: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/17673928>
294. Jack, G.S., *et al.* Current treatment options for penile fractures. *Rev Urol*, 2004. 6: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/16985591>
295. Cavalcanti, A.G., *et al.* Management of urethral lesions in penile blunt trauma. *Int J Urol*, 2006. 13: 1218.
<https://www.ncbi.nlm.nih.gov/pubmed/16984556>
296. Koraitim, M.M. Pelvic fracture urethral injuries: evaluation of various methods of management. *J Urol*, 1996. 156: 1288.
<https://www.ncbi.nlm.nih.gov/pubmed/8808856>
297. Leddy, L.S., *et al.* Outcomes of endoscopic realignment of pelvic fracture associated urethral injuries at a level 1 trauma center. *J Urol*, 2012. 188: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/22591965>
298. Moudouni, S.M., *et al.* Early endoscopic realignment of post-traumatic posterior urethral disruption. *Urology*, 2001. 57: 628.
<https://www.ncbi.nlm.nih.gov/pubmed/11306365>
299. Kulkarni, S.B., *et al.* Posterior urethral stricture after pelvic fracture urethral distraction defects in developing and developed countries, and choice of surgical technique. *J Urol*, 2010. 183: 1049.
<https://www.ncbi.nlm.nih.gov/pubmed/20092843>
300. Koraitim, M.M. Unsuccessful outcomes after posterior urethroplasty: definition, diagnosis, and treatment. *Urology*, 2012. 79: 1168.
<https://www.ncbi.nlm.nih.gov/pubmed/22449452>
301. Sofer, M., *et al.* Long-term results of early endoscopic realignment of complete posterior urethral disruption. *J Endourol*, 2010. 24: 1117.
<https://www.ncbi.nlm.nih.gov/pubmed/20590470>
302. Singh, B.P., *et al.* Impact of prior urethral manipulation on outcome of anastomotic urethroplasty for post-traumatic urethral stricture. *Urology*, 2010. 75: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/19854488>
303. Lumen, N., *et al.* Perineal anastomotic urethroplasty for posttraumatic urethral stricture with or without previous urethral manipulations: a review of 61 cases with long-term followup. *J Urol*, 2009. 181: 1196.
<https://www.ncbi.nlm.nih.gov/pubmed/19152939>
304. Mundy, A.R. The role of delayed primary repair in the acute management of pelvic fracture injuries of the urethra. *Br J Urol*, 1991. 68: 273.
<https://www.ncbi.nlm.nih.gov/pubmed/1913069>
305. Aboutaieb, R., *et al.* [Surgical treatment of traumatic ruptures of the posterior urethra]. *Prog Urol*, 2000. 10: 58.
<https://www.ncbi.nlm.nih.gov/pubmed/10785920>
306. Sfaxi, M., *et al.* [Surgical treatment of post-traumatic complete urethral rupture: deferred urgent urethral suture or delayed repair?]. *Prog Urol*, 2006. 16: 464.
<https://www.ncbi.nlm.nih.gov/pubmed/17069041>
307. Elliott, D.S., *et al.* Long-term followup and evaluation of primary realignment of posterior urethral disruptions. *J Urol*, 1997. 157: 814.
<https://www.ncbi.nlm.nih.gov/pubmed/9072573>
308. Culty, T., *et al.* Anastomotic urethroplasty for posttraumatic urethral stricture: previous urethral manipulation has a negative impact on the final outcome. *J Urol*, 2007. 177: 1374.
<https://www.ncbi.nlm.nih.gov/pubmed/17382735>

309. Webster, G.D., *et al.* Repair of pelvic fracture posterior urethral defects using an elaborated perineal approach: experience with 74 cases. *J Urol*, 1991. 145: 744.
<https://www.ncbi.nlm.nih.gov/pubmed/2005693>
310. Kizer, W.S., *et al.* Simplified reconstruction of posterior urethral disruption defects: limited role of supracrural rerouting. *J Urol*, 2007. 177: 1378.
<https://www.ncbi.nlm.nih.gov/pubmed/17382736>
311. Koraitim, M.M. On the art of anastomotic posterior urethroplasty: a 27-year experience. *J Urol*, 2005. 173: 135.
<https://www.ncbi.nlm.nih.gov/pubmed/15592055>
312. Cooperberg, M.R., *et al.* Urethral reconstruction for traumatic posterior urethral disruption: outcomes of a 25-year experience. *J Urol*, 2007. 178: 2006.
<https://www.ncbi.nlm.nih.gov/pubmed/17869302>
313. Koraitim, M.M. Optimising the outcome after anastomotic posterior urethroplasty. *Arab J Urol*, 2015. 13: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/26019975>
314. Koraitim, M.M., *et al.* Perineal repair of pelvic fracture urethral injury: in pursuit of a successful outcome. *BJU Int*, 2015. 116: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/24552421>
315. Webster, G.D., *et al.* Salvage posterior urethroplasty after failed initial repair of pelvic fracture membranous urethral defects. *J Urol*, 1990. 144: 1370.
<https://www.ncbi.nlm.nih.gov/pubmed/2231930>
316. MacDiarmid, S., *et al.* The importance of accurate assessment and conservative management of the open bladder neck in patients with post-pelvic fracture membranous urethral distraction defects. *Br J Urol*, 1995. 75: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/7850300>
317. Oosterlinck, W., *et al.* [Surgical treatment of urethral stenoses: technical aspects]. *Ann Urol (Paris)*, 2007. 41: 173.
<https://www.ncbi.nlm.nih.gov/pubmed/18260607>
318. Feng, C., *et al.* The relationship between erectile dysfunction and open urethroplasty: a systematic review and meta-analysis. *J Sex Med*, 2013. 10: 2060.
<https://www.ncbi.nlm.nih.gov/pubmed/23656595>
319. Levine, J., *et al.* Comparison of open and endoscopic treatment of posttraumatic posterior urethral strictures. *World J Surg*, 2001. 25: 1597.
<https://www.ncbi.nlm.nih.gov/pubmed/11775198>
320. Goel, M.C., *et al.* Endoscopic management of traumatic posterior urethral stricture: early results and followup. *J Urol*, 1997. 157: 95.
<https://www.ncbi.nlm.nih.gov/pubmed/8976224>
321. Singh, O., *et al.* Urogenital fistulas in women: 5-year experience at a single center. *Urol J*, 2010. 7: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/20209454>
322. Gokalp, A., *et al.* How to manage acute urethral false passage due to intermittent catheterization in spinal cord injured patients who refused insertion of an indwelling catheter. *J Urol*, 2003. 169: 203.
<https://www.ncbi.nlm.nih.gov/pubmed/12478136>
323. Maheshwari, P.N., *et al.* Immediate endoscopic management of complete iatrogenic anterior urethral injuries: a case series with long-term results. *BMC Urol*, 2005. 5: 13.
<https://www.ncbi.nlm.nih.gov/pubmed/16281970>
324. Pansadoro, V., *et al.* Iatrogenic prostatic urethral strictures: classification and endoscopic treatment. *Urology*, 1999. 53: 784.
<https://www.ncbi.nlm.nih.gov/pubmed/10197857>
325. Monga, M., *et al.* Testicular Trauma. *Adolesc Med*, 1996. 7: 141.
<https://www.ncbi.nlm.nih.gov/pubmed/10359963>
326. Frauscher, F., *et al.* US findings in the scrotum of extreme mountain bikers. *Radiology*, 2001. 219: 427.
<https://www.ncbi.nlm.nih.gov/pubmed/11323467>
327. de Peretti, F., *et al.* [Fuel tanks of motorcycles. Role in severe trauma of the pelvis]. *Presse Med*, 1993. 22: 61.
<https://www.ncbi.nlm.nih.gov/pubmed/8493205>
328. Herrmann, B., *et al.* Genital injuries in prepubertal girls from inline skating accidents. *Pediatrics*, 2002. 110: e16.
<https://www.ncbi.nlm.nih.gov/pubmed/12165615>

329. Lawson, J.S., *et al.* Catastrophic injuries to the eyes and testicles in footballers. *Med J Aust*, 1995. 163: 242.
<https://www.ncbi.nlm.nih.gov/pubmed/7565208>
330. Selikowitz, S.M. Penetrating high-velocity genitourinary injuries. Part I. Statistics mechanisms, and renal wounds. *Urology*, 1977. 9: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/855062>
331. Hudak, S.J., *et al.* Operative management of wartime genitourinary injuries at Balad Air Force Theater Hospital, 2005 to 2008. *J Urol*, 2009. 182: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/19450817>
332. Cass, A.S., *et al.* Bilateral testicular injury from external trauma. *J Urol*, 1988. 140: 1435.
<https://www.ncbi.nlm.nih.gov/pubmed/3193512>
333. McAninch, J.W., *et al.* Major traumatic and septic genital injuries. *J Trauma*, 1984. 24: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/6368854>
334. Michielsen, D., *et al.* Burns to the genitalia and the perineum. *J Urol*, 1998. 159: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/9649253>
335. Nelius, T., *et al.* Genital piercings: diagnostic and therapeutic implications for urologists. *Urology*, 2011. 78: 998.
<https://www.ncbi.nlm.nih.gov/pubmed/22054364>
336. Goldman, H.B., *et al.* Traumatic injuries of the female external genitalia and their association with urological injuries. *J Urol*, 1998. 159: 956.
<https://www.ncbi.nlm.nih.gov/pubmed/9474191>
337. Husmann, D.A. Editorial Comment. *J Urol* 1998. 159: 959.
[http://www.jurology.com/article/S0022-5347\(01\)63782-0/abstract](http://www.jurology.com/article/S0022-5347(01)63782-0/abstract)
338. Donovan, J.F., *et al.* The therapy of genital trauma by dog bite. *J Urol*, 1989. 141: 1163.
<https://www.ncbi.nlm.nih.gov/pubmed/2651716>
339. Presutti, R.J. Prevention and treatment of dog bites. *Am Fam Physician*, 2001. 63: 1567.
<https://www.ncbi.nlm.nih.gov/pubmed/11327433>
340. Talan, D.A., *et al.* Bacteriologic analysis of infected dog and cat bites. Emergency Medicine Animal Bite Infection Study Group. *N Engl J Med*, 1999. 340: 85.
<https://www.ncbi.nlm.nih.gov/pubmed/9887159>
341. Presutti, R.J. Bite wounds. Early treatment and prophylaxis against infectious complications. *Postgrad Med*, 1997. 101: 243.
<https://www.ncbi.nlm.nih.gov/pubmed/9126216>
342. Lewis, K.T., *et al.* Management of cat and dog bites. *Am Fam Physician*, 1995. 52: 479.
<https://www.ncbi.nlm.nih.gov/pubmed/7625323>
343. Dreesen, D.W., *et al.* Current recommendations for the prophylaxis and treatment of rabies. *Drugs*, 1998. 56: 801.
<https://www.ncbi.nlm.nih.gov/pubmed/9829154>
344. Anderson, C.R. Animal bites. Guidelines to current management. *Postgrad Med*, 1992. 92: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/1614928>
345. Gee, S., *et al.* Guidance for the Management of Human Bite Injuries. Health Protection Agency North West Policy Group, 2012.
http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947350692
346. Gaspar, S.S., *et al.* Sexual Urological Emergencies. *Sexual Medicine Reviews*, 2015. 3: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/27784550>
347. McGregor, M.J., *et al.* Sexual assault forensic medical examination: is evidence related to successful prosecution? *Ann Emerg Med*, 2002. 39: 639.
<https://www.ncbi.nlm.nih.gov/pubmed/12023707>
348. Okur, H., *et al.* Genitourinary tract injuries in girls. *Br J Urol*, 1996. 78: 446.
<https://www.ncbi.nlm.nih.gov/pubmed/8881959>
349. Dardamissis, E., *et al.* Guidance for healthcare professionals on dealing with injuries where teeth break the skin. Health Protection Agency North West Policy Group, 2007.
350. U.S. Department of Justice, Office on Violence Against Women. A National Protocol for Sexual Assault Medical Forensic Examinations: Adults/Adolescents. 2013:2nd edn.
<https://www.ncjrs.gov/pdffiles1/ovw/241903.pdf>
351. Amer, T., *et al.* Penile Fracture: A Meta-Analysis. *Urol Int*, 2016. 96: 315.
<https://www.ncbi.nlm.nih.gov/pubmed/26953932>
352. Haas, C.A., *et al.* Penile fracture and testicular rupture. *World J Urol*, 1999. 17: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/10367369>

353. Nicolaisen, G.S., *et al.* Rupture of the corpus cavernosum: surgical management. *J Urol*, 1983. 130: 917.
<https://www.ncbi.nlm.nih.gov/pubmed/6632099>
354. Tsang, T., *et al.* Penile fracture with urethral injury. *J Urol*, 1992. 147: 466.
<https://www.ncbi.nlm.nih.gov/pubmed/1732623>
355. Mydlo, J.H., *et al.* Urethrography and cavernosography imaging in a small series of penile fractures: a comparison with surgical findings. *Urology*, 1998. 51: 616.
<https://www.ncbi.nlm.nih.gov/pubmed/9586616>
356. Lee, S.H., *et al.* Trauma to male genital organs: a 10-year review of 156 patients, including 118 treated by surgery. *BJU Int*, 2008. 101: 211.
<https://www.ncbi.nlm.nih.gov/pubmed/17922859>
357. Karadeniz, T., *et al.* Penile fracture: differential diagnosis, management and outcome. *Br J Urol*, 1996. 77: 279.
<https://www.ncbi.nlm.nih.gov/pubmed/8800899>
358. Fedel, M., *et al.* The value of magnetic resonance imaging in the diagnosis of suspected penile fracture with atypical clinical findings. *J Urol*, 1996. 155: 1924.
<https://www.ncbi.nlm.nih.gov/pubmed/8618289>
359. Pretorius, E.S., *et al.* MR imaging of the penis. *Radiographics*, 2001. 21 Spec No: S283.
<https://www.ncbi.nlm.nih.gov/pubmed/11598264>
360. Uder, M., *et al.* MRI of penile fracture: diagnosis and therapeutic follow-up. *Eur Radiol*, 2002. 12: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/11868085>
361. Summerton, D.J., *et al.* Reconstructive surgery in penile trauma and cancer. *Nat Clin Pract Urol*, 2005. 2: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/16474736>
362. Penbegul, N., *et al.* No evidence of depression, anxiety, and sexual dysfunction following penile fracture. *Int J Impot Res*, 2012. 24: 26.
<https://www.ncbi.nlm.nih.gov/pubmed/21918532>
363. Orvis, B.R., *et al.* Penile rupture. *Urol Clin North Am*, 1989. 16: 369.
<https://www.ncbi.nlm.nih.gov/pubmed/2652861>
364. Virasoro, R., *et al.* Penile Amputation: Cosmetic and Functional Results. *Sexual Medicine Reviews*, 2015. 3: 214.
<https://www.ncbi.nlm.nih.gov/pubmed/27784611>
365. Babaei, A.R., *et al.* Penile replantation, science or myth? A systematic review. *Urol J*, 2007. 4: 62.
<https://www.ncbi.nlm.nih.gov/pubmed/17701923>
366. Lee, J.Y., *et al.* Traumatic dislocation of testes and bladder rupture. *Urology*, 1992. 40: 506.
<https://www.ncbi.nlm.nih.gov/pubmed/1466102>
367. Nagarajan, V.P., *et al.* Traumatic dislocation of testis. *Urology*, 1983. 22: 521.
<https://www.ncbi.nlm.nih.gov/pubmed/6649208>
368. Pollen, J.J., *et al.* Traumatic dislocation of the testes. *J Trauma*, 1982. 22: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/7069812>
369. Shefi, S., *et al.* Traumatic testicular dislocation: a case report and review of published reports. *Urology*, 1999. 54: 744.
<https://www.ncbi.nlm.nih.gov/pubmed/10754145>
370. Tiguert, R., *et al.* Management of shotgun injuries to the pelvis and lower genitourinary system. *Urology*, 2000. 55: 193.
<https://www.ncbi.nlm.nih.gov/pubmed/10688077>
371. Altarac, S. Management of 53 cases of testicular trauma. *Eur Urol*, 1994. 25: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/8137851>
372. Cass, A.S., *et al.* Value of early operation in blunt testicular contusion with hematocele. *J Urol*, 1988. 139: 746.
<https://www.ncbi.nlm.nih.gov/pubmed/3352037>
373. Cass, A.S., *et al.* Testicular injuries. *Urology*, 1991. 37: 528.
<https://www.ncbi.nlm.nih.gov/pubmed/2038785>
374. Wasko, R., *et al.* Traumatic rupture of the testicle. *J Urol*, 1966. 95: 721.
<https://www.ncbi.nlm.nih.gov/pubmed/5935538>
375. Andipa, E., *et al.* Magnetic resonance imaging and ultrasound evaluation of penile and testicular masses. *World J Urol*, 2004. 22: 382.
<https://www.ncbi.nlm.nih.gov/pubmed/15300391>

376. Corrales, J.G., *et al.* Accuracy of ultrasound diagnosis after blunt testicular trauma. *J Urol*, 1993. 150: 1834.
<https://www.ncbi.nlm.nih.gov/pubmed/8080482>
377. Fournier, G.R., Jr., *et al.* Scrotal ultrasonography and the management of testicular trauma. *Urol Clin North Am*, 1989. 16: 377.
<https://www.ncbi.nlm.nih.gov/pubmed/2652862>
378. Kratzik, C., *et al.* Has ultrasound influenced the therapy concept of blunt scrotal trauma? *J Urol*, 1989. 142: 1243.
<https://www.ncbi.nlm.nih.gov/pubmed/2681835>
379. Martinez-Pineiro, L., Jr., *et al.* Value of testicular ultrasound in the evaluation of blunt scrotal trauma without haematocele. *Br J Urol*, 1992. 69: 286.
<https://www.ncbi.nlm.nih.gov/pubmed/1568102>
380. Micalef, M., *et al.* Ultrasound features of blunt testicular injury. *Injury*, 2001. 32: 23.
<https://www.ncbi.nlm.nih.gov/pubmed/11164397>
381. Mulhall, J.P., *et al.* Emergency management of blunt testicular trauma. *Acad Emerg Med*, 1995. 2: 639.
<https://www.ncbi.nlm.nih.gov/pubmed/8521212>
382. Patil, M.G., *et al.* The value of ultrasound in the evaluation of patients with blunt scrotal trauma. *Injury*, 1994. 25: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/8168890>
383. Churukanti, G.R., *et al.* Role of Ultrasonography for Testicular Injuries in Penetrating Scrotal Trauma. *Urology*, 2016. 95: 208.
<https://www.ncbi.nlm.nih.gov/pubmed/27132505>
384. Muglia, V., *et al.* Magnetic resonance imaging of scrotal diseases: when it makes the difference. *Urology*, 2002. 59: 419.
<https://www.ncbi.nlm.nih.gov/pubmed/11880084>
385. Altarac, S. A case of testicle replantation. *J Urol*, 1993. 150: 1507.
<https://www.ncbi.nlm.nih.gov/pubmed/8411440>
386. Tchounzou, R., *et al.* Retrospective Analysis of Clinical Features, Treatment and Outcome of Coital Injuries of the Female Genital Tract Consecutive to Consensual Sexual Intercourse in the Limbe Regional Hospital. *Sex Med*, 2015. 3: 256.
<https://www.ncbi.nlm.nih.gov/pubmed/26797059>
387. Sotto, L.S., *et al.* Perigenital hematomas; analysis of forty-seven consecutive cases. *Obstet Gynecol*, 1958. 12: 259.
<https://www.ncbi.nlm.nih.gov/pubmed/13578292>
388. McWilliams, G.D., *et al.* Gynecologic emergencies. *Surg Clin North Am*, 2008. 88: 265.
<https://www.ncbi.nlm.nih.gov/pubmed/18381113>
389. Virgili, A., *et al.* Serious hematoma of the vulva from a bicycle accident. A case report. *J Reprod Med*, 2000. 45: 662.
<https://www.ncbi.nlm.nih.gov/pubmed/10986686>
390. Monstrey, S.J., *et al.* Urological trauma and severe associated injuries. *Br J Urol*, 1987. 60: 393.
<https://www.ncbi.nlm.nih.gov/pubmed/3427315>
391. MacKenzie, E.J., *et al.* A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med*, 2006. 354: 366.
<https://www.ncbi.nlm.nih.gov/pubmed/16436768>
392. Caterson, E.J., *et al.* Boston bombings: a surgical view of lessons learned from combat casualty care and the applicability to Boston's terrorist attack. *J Craniofac Surg*, 2013. 24: 1061.
<https://www.ncbi.nlm.nih.gov/pubmed/23851738>
393. Dutton, R.P., *et al.* Daily multidisciplinary rounds shorten length of stay for trauma patients. *J Trauma*, 2003. 55: 913.
<https://www.ncbi.nlm.nih.gov/pubmed/14608165>
394. Makanjuola, J.K., *et al.* Centralisation of major trauma: an opportunity for acute urology services in the UK. *BJU Int*, 2012. 109: 173.
<https://www.ncbi.nlm.nih.gov/pubmed/22212283>
395. Feliciano DV, Moore EE., Mattox KL., Trauma damage control, in *Trauma*, Feliciano DV, Mattox KL, Moore EE, Eds. 2000, McGraw-Hill: New York.
396. Hirshberg, A., *et al.* 'Damage control' in trauma surgery. *Br J Surg*, 1993. 80: 1501.
<https://www.ncbi.nlm.nih.gov/pubmed/8298911>

397. Rignault, D.P. Recent progress in surgery for the victims of disaster, terrorism, and war--Introduction. *World J Surg*, 1992. 16: 885.
<https://www.ncbi.nlm.nih.gov/pubmed/1462624>
398. Rotondo, M.F., *et al.* 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma*, 1993. 35: 375.
<https://www.ncbi.nlm.nih.gov/pubmed/8371295>
399. Mercer, S.J., *et al.* Lessons from the battlefield: human factors in defence anaesthesia. *Br J Anaesth*, 2010. 105: 9.
<https://www.ncbi.nlm.nih.gov/pubmed/20551025>
400. Holcomb, J.B., *et al.* Military, civilian, and rural application of the damage control philosophy. *Mil Med*, 2001. 166: 490.
<https://www.ncbi.nlm.nih.gov/pubmed/11413725>
401. Brandes, S.B., *et al.* Renal trauma: a practical guide to evaluation and management. *ScientificWorldJournal*, 2004. 4 Suppl 1: 31.
<https://www.ncbi.nlm.nih.gov/pubmed/15349524>
402. Hirshberg A, M.K., *Top Knife: the Art and Craft of Trauma Surgery*. 2005, TFM Publishing Ltd. : Shrewsbury, UK.
<http://www.tfmpublishing.com/top-knife-the-art-craft-of-trauma-surgery>
403. Best, C.D., *et al.* Traumatic ureteral injuries: a single institution experience validating the American Association for the Surgery of Trauma-Organ Injury Scale grading scale. *J Urol*, 2005. 173: 1202.
<https://www.ncbi.nlm.nih.gov/pubmed/15758748>
404. Hirshberg, A., *et al.* Planned reoperation for trauma: a two year experience with 124 consecutive patients. *J Trauma*, 1994. 37: 365.
<https://www.ncbi.nlm.nih.gov/pubmed/8083894>
405. Gomez, R.G., *et al.* Consensus statement on bladder injuries. *BJU Int*, 2004. 94: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/15217426>
406. van der Horst, C., *et al.* Male genital injury: diagnostics and treatment. *BJU Int*, 2004. 93: 927.
<https://www.ncbi.nlm.nih.gov/pubmed/15142139>
407. Gross, M. Rupture of the testicle: the importance of early surgical treatment. *J Urol*, 1969. 101: 196.
<https://www.ncbi.nlm.nih.gov/pubmed/5765482>
408. Slater, M.S., *et al.* Terrorism in America. An evolving threat. *Arch Surg*, 1997. 132: 1059.
<https://www.ncbi.nlm.nih.gov/pubmed/9336502>
409. Caro, D. Major disasters. *Lancet*, 1974. 2: 1309.
<https://www.ncbi.nlm.nih.gov/pubmed/4139541>
410. Weight, J.A., *et al.* American College of Surgeons Committee on Trauma, Advanced Trauma Life Support Student Course Manual. 6th, ed. 1997, Chicago.
411. National Audit Office, *Treating Injury and Illness arising on Military Operations*. February 2010.
<https://www.nao.org.uk/report/ministry-of-defence-treating-injury-and-illness-arising-on-military-operations/>
412. Frykberg, E.R. Medical management of disasters and mass casualties from terrorist bombings: how can we cope? *J Trauma*, 2002. 53: 201.
<https://www.ncbi.nlm.nih.gov/pubmed/12169923>
413. Jacobs, L.M., Jr., *et al.* An emergency medical system approach to disaster planning. *J Trauma*, 1979. 19: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/458880>

7. CONFLICT OF INTEREST

All members of the Urological Trauma Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://uroweb.org/guidelines/>. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Chronic Pelvic Pain

D. Engeler (Chair), A.P. Baranowski, J. Borovicka,
A.M. Cottrell, P. Dinis-Oliveira, S. Elneil, J. Hughes,
E.J. Messelink (Vice-chair), A.C. de C Williams
Guidelines Associates: S. Goonewardene, M.P. Schneider

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1. INTRODUCTION

1.1 Aim

This guideline plays an important role in the process of consolidation and improvement of care for patients with abdominal and pelvic pain. From both literature and daily practice it has become clear that abdominal and pelvic pain are areas still under development. This guideline has been recognised as a cornerstone for important developments that have taken place in the past ten years.

This guideline aims to expand the awareness of caregivers in the field of abdominal and pelvic pain and to assist those who treat patients with abdominal and pelvic pain in their daily practice. The guideline is a useful instrument not only for urologists, but also for gynaecologists, surgeons, physiotherapists, psychologists and pain doctors.

It must be emphasised that clinical guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

Structure and scope

The panel wishes to take advantage of modern methods of delivering guideline information to clinicians dealing with these patients. In 2016, we made a stepped information structure, in alignment with stepped care protocols, using new digital information sources like websites and apps to aid this process. Furthermore, the guideline was changed according to the template used in all other non-oncology guidelines of the EAU. It was recognised that structuring a guideline on chronic pain is quite different from structuring one on another subject. A multi-disciplinary approach is of utmost importance and demands a broad view. In 2016, the guideline was rewritten in such a way that it is centred around pain instead of being organ-centred. It is partly theoretical to show the importance of using this pain centred approach. The biggest part, however, deals with the practical approach to diagnostics, treatment and management of patients with abdominal and pelvic pain.

1.2 Publication history

The EAU Guidelines on Chronic Pelvic Pain were first published in 2003 [1] which formed the basis of a scientific publication in European Urology in 2004 [2]. Also, in the 2003 edition the concept of Chronic Pelvic Pain Syndromes (CPPS) was introduced, which is now referred to as “pain as a disease process”. Partial updates of the CPP Guidelines were published in 2008 and formed the basis for another scientific publication in European Urology in the year 2010 [3, 4].

Two chapters were added at that time: Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 7 ‘Sexological aspects of chronic pelvic pain’. In the 2014 edition minor revisions were made in Chapters 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and 8 ‘Psychological aspects of chronic pelvic pain’.

For the 2015 edition the Panel critically reviewed the sub-chapter on bladder pain syndrome which is now a comprehensive part of the guideline [5].

In 2016, the guideline was rewritten in such a way that it is centred around pain instead of being organ-centred and furthermore restructured in accordance with the template used in all other non-oncology guidelines of the EAU.

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available, presenting key findings of the Chronic Pelvic Pain Guidelines. This reference document follows the updating cycle of the underlying large texts. All available material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of EAU Guideline articles as well as translations produced by national urological associations: <http://www.uroweb.org/guidelines/online-guidelines/>.

1.4 Panel composition

The panel of experts responsible for this document include four urologists, (one of which has a sub-specialisation in neuro-urology and one is a sexologist), two consultants in pain medicine, a gynaecologist, a psychologist and a gastroenterologist.

The Panel is also grateful to Dr. N. Wood for his expertise, time and diligence in undertaking a review of these Guidelines from a patient perspective.

1.5 Terminology

Definitions of CPP terminology

Classification

Much debate over the classification of CPP has occurred, is ongoing and will continue in the future. Classification involves three aspects of defining a condition: phenotyping, terminology and taxonomy.

Phenotyping

Phenotyping is describing the condition. For example, chronic bladder pain may be associated with the presence of Hunner's ulcers and glomerulation on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for irritable bowel syndrome (IBS), which may be sub-divided into that associated primarily with diarrhoea or that with constipation. Phenotyping is based upon mechanisms when they are known (e.g., infection, ischaemic, autoimmune, or neuropathic). In the absence of well-defined mechanisms, describing the condition by its symptoms, signs and, where possible, by investigations, has been demonstrated to have clinical and research validity in many situations. When pain is the main symptom and pain as a disease process is considered the cause, the condition is often referred to as a pain syndrome - a well-defined collection of symptoms, signs and investigation results associated with pain mechanisms and pain perception as the primary complaint.

Terminology

Terminology is the words that are used within classification, both to name the phenotype and within the definition of the phenotype. Examples of names for phenotypes associated with the bladder include interstitial cystitis, painful bladder syndrome or bladder pain syndrome (BPS). The EAU, the International Society for the study of BPS (ESSIC), the International Association for the Study of Pain (IASP) and several other groups now prefer the term bladder pain syndrome. In the pain syndromes, the role of the nervous system in generating the sensations is thought to be pivotal, but the term syndrome is also comprehensive and takes into account the emotional, cognitive, behavioural, sexual and functional consequences of the chronic pain.

When defining the phenotype, the terminology used in that definition must also be clear and if necessary defined. One of the most important guiding principles is that spurious terminology should be avoided. Terms that end in "itis" in particular should be avoided unless infection and or inflammation is proven and considered to be the cause of the pain [6]. It must be appreciated that end-organ inflammation may be secondary and neurogenic in origin and not a primary cause of the pain.

Taxonomy

Taxonomy places the phenotypes into a relationship hierarchy. The EAU approach sub-divides CPP into conditions that are pain syndromes and those that are non-pain syndromes. The latter are conditions that have well-recognised pathology (e.g., infection, neuropathy or inflammation), whereas the former syndromes do not and pain as a disease process is the mechanism. Other terms for the non-pain syndromes include "classical conditions", "well-defined conditions" and "confusable diseases". Although the EAU approach deals primarily with urological conditions, this approach to classification can be applied to all conditions associated with pain perception within the pelvis; the classification has been developed to include non-urological pain and was accepted by the IASP for publication in January 2012.

Classification of CPP syndromes

Importance of classification

It should be obvious to all that a condition cannot be treated unless it is defined. However, the reasons for classifying CPP go far beyond that.

Clues to the mechanism

As a result of systematic phenotypic and taxonomic classifications, similarities and differences between conditions become clear. Drawing comparisons between the phenotypes of different disorders allows one to compare disorders such as bladder and bowel pain syndromes, thus facilitating research and treatment.

Guidelines for best treatment options

As conditions become better defined, more specific treatment approaches can be adopted. In particular, there

will be a move away from treatments based upon spurious terms (e.g., antibiotics and non-steroidal anti-inflammatory drugs for the “-itis” conditions). Generic treatments aimed at groups of conditions will be more commonplace and based upon research evidence.

Research platform

Only by clearly defining the phenotype being investigated can research be valued or applied to the clinical situation.

Patient needs

A diagnosis, or name, for a set of symptoms can provide patients with a sense of being understood, as well as hope for relief. It may therefore help in acceptance of the problem as chronic, resolution of unfounded fears about its implications (if not life-threatening), and engagement in therapeutic endeavours, as well as in self-management. However, it may also lead to accessing information of variable quality associated with the diagnosis or name, and the possibility of generating new concerns about long-term consequences or about appropriateness of treatment.

IASP definitions

Sub-dividing pain syndromes

There is much debate on the sub-divisions of the pain syndromes within the hierarchical taxonomy. The EAU has led the way in this regard and the guiding principles are as follows [2]:

1. The pain syndromes are defined by a process of exclusion. In particular, there should be no evidence of infection or inflammation. Investigations by end-organ specialists should therefore be aimed at obtaining a differential diagnosis; repeated, unnecessary investigations are detrimental in the management of chronic pain syndromes.
2. A sub-division phenotype should only be used if there is adequate evidence to support its use. For instance, in non-specific, poorly localised pelvic pain without obvious pathology, only the term chronic pelvic pain syndrome (CPPS) should be used. If the pain can be localised to an organ, then a more specific term, such as rectal pain syndrome, may be used. If the pain is localised to multiple organs, then the syndrome is a regional pain syndrome and the term CPPS should once again be considered. As well as defining the patient by a specific end-organ phenotype, there are several other more general descriptors that need to be considered. These are primarily psychological (e.g., cognitive or emotional), sexual, behavioural and functional. Psychological and behavioural factors are well-established factors which relate to quality of life (QoL) issues and prognosis. In North America a research programme, the MAPP program (Multi-disciplinary Approach to the study of Chronic Pelvic Pain research) has been devised to investigate the importance of these factors and looks at all types of pelvic pain irrespective of the end-organ where the pain is perceived. It also looks at systemic disorder associations, such as the co-occurrence of fibromyalgia, facial pain, or auto-immune disorders.
3. In 2004 this expert panel introduced the concept of managing the polysymptomatic nature of CPP, since then others have developed their own schemes, such as Nickel's UPOINT [7], modified by Magri *et al.* [8]. In light of these and other publications, the symptom classification table has been updated (Table 1).

The debate in relation to sub-dividing the pain syndromes remains ongoing. As more information is collected suggesting that the central nervous system (CNS) is involved, and indeed may be the main cause of many CPP conditions (e.g., bladder, genitalia, colorectal or myofascial), there is a general tendency to move away from end-organ nomenclature. Only time and good research will determine whether this is appropriate. To enable such research, it is essential to have a framework of classification within which to work. Any hierarchical taxonomy must be flexible to allow change.

In Table 1 the classification has been set up according to the axis system used by IASP.

Table 1: EAU classification of chronic pelvic pain syndromes

Axis I Region	Axis II System	Axis III End-organ as pain syndrome as identified from Hx, Ex and Ix	Axis IV Referral characteristics	Axis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
Chronic pelvic pain	Urological	Prostate	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Bladder					
OR	Gynaecological	Scrotal Testicular Epididymal	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Penile Urethral					
Pelvic pain syndrome	Gastrointestinal	Postvasectomy	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Vulvar Vestibular Clitoral					
Pelvic pain syndrome	Peripheral nerves	Endometriosis associated	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		CPPS with cyclical exacerbations					
Pelvic pain syndrome	Sexological	Dysmenorrhoea	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Irritable bowel					
Pelvic pain syndrome	Psychological	Chronic anal	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Intermittent chronic anal					
Musculo-skeletal	Musculo-skeletal	Pudendal pain syndrome	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Dyspareunia					
Musculo-skeletal	Musculo-skeletal	Pelvic pain with sexual dysfunction	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Any pelvic organ					
Musculo-skeletal	Musculo-skeletal	Any pelvic organ	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Pelvic floor muscle Abdominal muscle Spinal					
Musculo-skeletal	Musculo-skeletal	Coccyx	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitance Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloating Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance

Hx = History; Ex = Examination; Ix = Investigation; PTSD = post-traumatic stress disorder.

Pain syndromes

The original EAU classification [2] was inspired by the IASP classification [9] and much work around what has become known as “pain as a disease” and its associated psychological, behavioural, sexual and functional correlates. After ten years of work developing the initial ideas, an updated version was accepted by IASP Council for publication in January 2012.

Definition of chronic pelvic pain (CPP)

Chronic pelvic pain is chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction. [*Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) has localised the pain as being perceived in a specified anatomical pelvic area.]

In the case of documented nociceptive pain that becomes chronic/persistent through time, pain must have been continuous or recurrent for at least six months. That is, it can be cyclical over a six-month period, such as the cyclical pain of dysmenorrhoea. Although arbitrary, six months was chosen because three months was not considered long enough if cyclical pain conditions are included. If non-acute and central sensitisation pain mechanisms are well documented, then the pain may be regarded as chronic, irrespective of the time period. Cyclical pain is included in the classification and hence dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual, or emotional consequences.

Chronic pelvic pain may be sub-divided into conditions with well-defined classical pathology (such as infection or cancer) and those with no obvious pathology. For the purpose of this classification, the term “specific disease-associated pelvic pain” is proposed for the former, and “chronic pelvic pain syndrome” for the latter. The following classification only deals with Chronic Pelvic Pain Syndrome.

Definition of chronic pelvic pain syndrome (CPPS)

Chronic pelvic pain syndrome is the occurrence of CPP when there is no proven infection or other obvious local pathology that may account for the pain. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. CPPS is a sub-division of CPP.

Further subdivision of CPPS

Pain perception in CPPS may be focused within a single organ, more than one pelvic organ and even associated with systemic symptoms such as chronic fatigue syndrome (CFS), fibromyalgia (FM) or Sjögren's syndrome. When the pain is localised to a single organ, some specialists may wish to consider using an end organ term such as BPS (Table 2). The use of such a phrase with the terminology “syndrome” indicates that, although peripheral mechanisms may exist, CNS neuromodulation may be more important and systemic associations may occur. When the pain is localised to more than one organ site, the term CPPS should be used. Many, including some of the authors of this text, never sub-divide by anatomy and prefer to refer to patients with pain perceived within the pelvis, and no specific disease process, as suffering from CPPS, sub-divided by psychological and functional symptoms.

Psychological considerations for classification

Many CPPSs are associated with a range of concurrent negative psychological, behavioural and sexual consequences that must be described and assessed. Examples that need to be considered are depression, anxiety, fears about pain or its implications, unhelpful coping strategies, and distress in relationships. Both anxiety and depression can be significant important concomitant symptoms that are relevant to pain, disability and poor QoL. Catastrophic interpretation of pain has been shown to be a particularly salient variable, predicting patients' report of pain, disability, and poor QoL, over and above psychosocial variables such as depression or behavioural factors such as self-reported sexual dysfunction. It is suggested that CPPS sometimes creates a sense of helplessness that can be reported as overwhelming, and may be associated with the refractory nature of the patients' symptoms. It is important to note that many of these bio-psychosocial consequences are common to other persistent pain problems but may show varying degrees of importance for any one individual suffering from CPPS. In all patients with CPPS, these consequences must be clearly described as part of the phenotype (where the term phenotype is used to indicate the observable characteristics of the syndrome).

Functional considerations for classification

Functional disorders, for the purpose of this document, are pathologies that have arisen secondary to changes in the control mechanisms of an organ or system. That is, they are disorders characterised by disturbance of function. As an example, slow colonic transit is a functional disorder of the bowel - the normal function of the bowel is not occurring as a result of changes in the mechanisms that produce defecation, and hence bowel control is abnormal. The term is not used in the sense of a psychiatric functional disorder. Many CPPSs are associated with functional abnormalities at a local and even systemic level. These also need to be defined as a part of the phenotype.

Functional pain disorders may not express significant pathology in the organs that appear responsible for the primary symptoms, but they are associated with substantial neurobiological, physiological and sometimes anatomical changes in the CNS.

Multi-system sub-division

It is recognised that the end-organ where the pain is perceived may not be the centre of pain generation. This classification is based upon the most effective and accepted method of classifying and identifying different pain syndromes, that is, by site of presentation. It is argued that keeping the end-organ name in the classification is inappropriate because, in most cases, there are multi-systemic causes and effects, with the result that symptoms are perceived in several areas. This is an area in which discussions are ongoing, and despite there being strong arguments for both keeping and dispensing with end-organ classification, the authors have not taken the umbrella approach of referring to all pain perceived in the pelvis as CPPS.

Dyspareunia

Dyspareunia is defined as pain perceived within the pelvis associated with penetrative sex. It tells us nothing about the mechanism and may be applied to women and men. It is usually applied to penile penetration, but is often associated with pain during insertion of any object. It may apply to anal as well as vaginal intercourse. It is classically sub-divided into superficial and deep.

Perineal pain syndrome

Perineal pain syndrome is a neuropathic-type pain that is perceived in the distribution area of the pudendal nerve, and may be associated with symptoms and signs of rectal, urinary tract or sexual dysfunction. There is no proven obvious pathology. It is often associated with negative cognitive, behavioural, sexual and emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Perineal pain syndrome should be distinguished from pudendal neuralgia, which is a specific disease associated with pelvic pain that is caused by nerve damage.

Table 2: Chronic Pelvic Pain Syndromes

Urological Pain Syndromes	
Prostate pain syndrome	Prostate pain syndrome (PPS) is the occurrence of persistent or recurrent episodic pain (which is convincingly reproduced by prostate palpation). There is no proven infection or other obvious local pathology. PPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. The term “chronic prostatitis” continues to be equated with that of PPS. In the authors’ and others’ opinion, this is an inappropriate term, although it is recognised that it has a long history of use. The National Institutes of Health (NIH) consensus [10] includes infection (types I and II), which the authors feel should not be considered under PPS, but as specific disease-associated pelvic pain. The term prostaticodynia has also been used in the past but is no longer recommended by the expert panel. Please note that some of the authors of the IASP document disagree with this term and suggest that CPPS of the male is used instead of PPS, which has been agreed by the majority.
Bladder pain syndrome	Bladder pain syndrome (BPS) is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. BPS is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. BPS is believed to represent a heterogeneous spectrum of disorders. There may be specific types of inflammation as a feature in subsets of patients. Localisation of the pain can be difficult by examination, and consequently, another localising symptom is required. Cystoscopy with hydrodistension and biopsy may be indicated to define phenotypes. Recently, ESSIC has suggested a standardised scheme of sub-classifications [11] to acknowledge differences and make it easier to compare various studies. Other terms that have been used include “interstitial cystitis”, “painful bladder syndrome”, and “PBS/IC” or “BPS/IC”. These terms are no longer recommended.
Scrotal pain syndrome	Scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised within the organs of the scrotum, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Scrotal pain syndrome is a generic term and is used when the site of the pain is not clearly testicular or epididymal. The pain is not in the skin of the scrotum as such, but perceived within its contents, in a similar way to idiopathic chest pain.
Testicular pain syndrome	Testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended.
Epididymal pain syndrome	Epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences.
Penile pain syndrome	Penile pain syndrome is the occurrence of pain within the penis that is not primarily in the urethra, in the absence of proven infection or other obvious local pathology. Penile pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.

Urethral pain syndrome	Urethral pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the urethra, in the absence of proven infection or other obvious local pathology. Urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Urethral pain syndrome may occur in men and women.
Post-vasectomy scrotal pain syndrome	Post-vasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy. Post-vasectomy scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Post-vasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and for that reason it is considered a special form of scrotal pain syndrome.
Gynaecological Pain Syndromes: external genitalia	
Vulvar pain syndrome	Vulvar pain syndrome is the occurrence of persistent or recurrent episodic vulvar pain. There is no proven infection or other local obvious pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Although pain perceived in the vulva was included under sexual disorders in the DSM-IV-R manual for classifying psychiatric disorders, there is no scientific basis for this classification, and pain perceived in the vulva is best understood as a pain problem that usually has psychological consequences. There is no evidence for its classification as a psychiatric disorder. The International Society for the Study of Vulvovaginal Disease (ISSVD) has used the term vulvodynia, where we use the term vulvar pain syndrome. According to the ISSVD, vulvodynia is vulvar pain that is not accounted for by any physical findings. The ISSVD has defined vulvodynia as “vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder”. If physical findings are present, the patient is said to have vulvar pain due to a specified cause. The ISSVD has sub-divided vulvodynia based on pain location and temporal characteristics of the pain (e.g. provoked or unprovoked). The following definitions are based on that approach.
Generalised vulvar pain syndrome	Generalised vulvar pain syndrome refers to a vulvar pain syndrome in which the pain/burning cannot be consistently and precisely localised by point-pressure mapping via probing with a cotton-tipped applicator or similar instrument. Rather, the pain is diffuse and affects all parts of the vulva. The vulvar vestibule (the part that lies between the labia minora into which the urethral meatus and vaginal introitus open) may be involved but the discomfort is not limited to the vestibule. This pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included “dysesthetic vulvodynia” and “essential vulvodynia”, but are no longer recommended.
Localised vulvar pain syndrome	Localised vulvar pain syndrome refers to pain that can be consistently and precisely localised by point-pressure mapping to one or more portions of the vulva. Clinically, the pain usually occurs as a result of provocation (touch, pressure or friction). Localised vulvar pain syndrome can be sub-divided into vestibular pain syndrome and clitoral pain syndrome.
Vestibular pain syndrome	Vestibular pain syndrome refers to pain that can be localised by point-pressure mapping to the vestibule or is well perceived in the area of the vestibule.
Clitoral pain syndrome	Clitoral pain syndrome refers to pain that can be localised by point-pressure mapping to the clitoris or is well-perceived in the area of the clitoris.

Gynaecological system: internal pelvic pain syndromes	
Endometriosis-associated pain syndrome	Endometriosis-associated pain syndrome is chronic or recurrent pelvic pain in patients with laparoscopically confirmed endometriosis, and the term is used when the symptoms persist despite adequate endometriosis treatment. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Many patients have pain above and beyond the endometriotic lesions; this term is used to cover that group of patients. Endometriosis may be an incidental finding, is not always painful, and the degree of disease seen laparoscopically does not correlate with severity of symptoms. As with other patients, they often have more than one end-organ involved. It has been suggested that this phenotype should be removed from the classification because the endometriosis may be irrelevant.
Chronic pelvic pain syndrome with cyclical exacerbations	Chronic pelvic pain syndrome with cyclical exacerbations covers the non-gynaecological organ pain that frequently shows cyclical exacerbations (e.g., IBS or BPS) as well as pain similar to that associated with endometriosis/adenomyosis but where no pathology is identified. This condition is different from dysmenorrhoea, in which pain is only present with menstruation.
Dysmenorrhoea	Dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences.
Gastrointestinal Pelvic Pain Syndromes	
Irritable bowel syndrome (IBS)	IBS is the occurrence of chronic or recurrent episodic pain perceived in the bowel, in the absence of proven infection or other obvious local pathology. Bowel dysfunction is frequent. IBS is often associated with worry and pre-occupation about bowel function, and negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract or gynaecological dysfunction. The above classification is based upon the Rome III Criteria [12]: three months of continuous or recurring symptoms of abdominal pain or irritation that may be relieved with a bowel movement, may be coupled with a change in frequency, or may be related to a change in stool consistency. Two or more of the following are present at least 25% of the time: change in stool frequency (> three bowel movements per day or < three per week); noticeable difference in stool form (hard, loose, watery or poorly formed stools); passage of mucus in stools; bloating or feeling of abdominal distension; or altered stool passage (e.g., sensation of incomplete evacuation, straining, or urgency). Extra-intestinal symptoms include: nausea, fatigue, full sensation after even a small meal, and vomiting.
Chronic anal pain syndrome	Chronic anal pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the anus, in the absence of proven infection or other obvious local pathology. Chronic anal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction.
Intermittent chronic anal pain syndrome	Intermittent chronic anal pain syndrome refers to severe, brief, episodic pain that seems to arise in the rectum or anal canal and occurs at irregular intervals. This is unrelated to the need to or the process of defecation. It may be considered a sub-group of the chronic anal pain syndromes. It was previously known as "proctalgia fugax" but this term is no longer recommended.
Musculoskeletal System	
Pelvic floor muscle pain syndrome	Pelvic floor muscle pain syndrome is the occurrence of persistent or recurrent episodic pelvic floor pain. There is no proven well-defined local pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. This syndrome may be associated with over-activity of or trigger points within the pelvic floor muscles. Trigger points may also be found in several muscles, such as the abdominal, thigh and paraspinal muscles and even those not directly related to the pelvis.

Coccyx pain syndrome	Coccyx pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the region of the coccyx, in the absence of proven infection or other obvious local pathology. Coccyx pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. The term “coccydynia” was used but is no longer recommended.
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2. METHODOLOGY

2.1 Methods

References used in this text are assessed according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence [13]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: <http://www.uroweb.org/guideline/>. A list of Associations endorsing the EAU Guidelines can also be reviewed online at the above address.

The 2012 full text update was based on a systematic review of literature using the Embase and Medline databases, the Cochrane Central Register of controlled trials and the PsycINFO and Bandolier databases to identify the best evidence from randomised controlled trials (RCTs) (Level of Evidence 1 (LE: 1)) according to the rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence [13]. Where no LE: 1 literature could be identified the search was moved down to the next lower level on the rating scale. Extensive use of free text ensured the sensitivity of the searches, resulting in a substantial body of literature to scan. Searches covered the period January 1995 to July 2011 and were restricted to English language publications.

For the 2017 print, a scoping search was performed, covering all areas of the guideline starting from the last cut-off date of July 2011 with a cut-off date of May 2016. Embase, Medline, the Cochrane Central Register of Controlled Trials and CINAHL databases were searched and were restricted to English language publications. A total of 3,489 unique records were identified, retrieved and screened for relevance of which 47 publications were selected for inclusion in the 2017 guidelines. A detailed search strategy is available online: <https://uroweb.org/guideline/chronic-pelvic-pain/>. The gynaecological aspects of the guideline were not updated in this edition but will be updated in 2018.

2.2 Review

This document was subject to peer review prior to publication in 2015.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2018 update of the Chronic Pelvic Pain Guidelines. An ongoing systematic review is:

- What are the benefits and harms of electrical neuromodulation vs. best clinical practice or no treatment in CPP? [14].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

3.1 Chronic visceral pain

Definition of pain

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP Taxonomy).

Introduction to chronic pelvic pain syndromes

Over the years much of the focus for CPP has been on peripheral-end-organ mechanisms, such as inflammatory or infective conditions. However, both animal and clinical research have indicated that many of

the mechanisms for the CPP syndromes are based within the CNS. Although a peripheral stimulus such as infection may initiate the start of a CPP condition, the condition may become self-perpetuating as a result of CNS modulation. As well as pain, these central mechanisms are associated with several other sensory, functional, behavioural and psychological phenomena. It is this collection of phenomena that forms the basis of the pain syndrome diagnosis and each individual phenomena needs to be addressed in its own right through multi-specialty and multi-disciplinary care. Although ongoing peripheral organ pathology can produce persistent and chronic pain, the main focus of these guidelines is on CPP syndromes in which no peripheral ongoing pathology (such as infection or neoplastic disease) is detected. The main exception is when pain is due to peripheral nerve damage.

3.1.1 **Incidence**

No adequate data on incidence were found.

3.1.2 **Prevalence**

In a large study in Europe undertaken in 2004 [15] it was found that chronic pain of moderate to severe intensity occurs in 19% of adult Europeans, seriously affecting the quality of their social and working lives. There are some differences between countries but not much spread is seen.

3.1.3 **Influence on Quality of Life**

Assessing the QoL in pelvic pain patients is challenging due to the multi-faceted nature of the complaints and the overlap between the different pelvic pain syndromes [16]. Assessment of QoL is further complicated due to the complex pathology of pain itself [17].

Pelvic pain syndromes do have an impact on QoL [18, 19]. This may result in depression, anxiety, impaired emotional functioning, insomnia and fatigue [18, 20]. If these aspects are identified and targeted early in the diagnostic process, the associated pain symptoms may also improve [21]. Addressing co-morbidities will help in further improving QoL [22]. Quality of life assessment is therefore important in patients with pelvic pain and should include physical, psychosocial and emotional tools, using standardised and validated instruments [19].

The impact of pain on QoL has been assessed in an extensive European study [15]. In-depth interviews with 4,839 respondents with chronic pain (about 300 per country) showed: 66% had moderate pain (NRS = 5-7) and 34% had severe pain (NRS = 8-10), 46% had constant pain, 54% had intermittent pain. 59% had suffered with pain for two to fifteen years, 21% had been diagnosed with depression because of their pain, 61% were less able or unable to work outside their home, 19% had lost their job and 13% had changed jobs because of their pain. 60% visited their doctor about their pain two to nine times in the last six months. Only 2% were currently treated by a pain management specialist.

3.1.4 **Costs**

No adequate data on costs were found.

3.1.5 **Risk Factors and underlying causes**

3.1.5.1 **Risk factors**

Risk factors include many different factors from various areas, including genetic, psychological state, recurrent physical trauma and endocrine factors.

The endocrine system is involved in visceral function. Significant life events, and in particular, early life events may alter the development of the hypothalamic-pituitary-adrenal axis and the chemicals released. Increased vulnerability to stress is thought to be partly due to increased corticotrophin-releasing hormone (CRH) gene expression. Up-regulation of CRH has been implicated in several pain states such as rectal hypersensitivity to rectal distension. This model suggests an action of CRH on mast cells. A range of stress-related illnesses have been suggested, e.g. IBS and BPS. There is evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception. Stress can also produce long-term biological changes which may form the relation between chronic pain syndromes and significant early life and adverse life events [23]. Asking the patient about these events is important as they have an effect on a patient's psychological wellbeing [24-26].

Genetics also play a role in assessing the risk of developing chronic pain. An individual who has one chronic pain syndrome is more likely to develop another. Family clusters of pain conditions are also observed and animals can be bred to be more prone to apparent chronic pain state. A range of genetic variations have been described that may explain the pain in certain cases; many of these are to do with subtle changes

in transmitters and their receptors. However, the picture is more complicated in that developmental, environmental and social factors also influence the situation. Evidence that BPS may have a genetic component has been presented in several identical twin studies, but genetics may contribute to less than one third of total variation in susceptibility to BPS [27, 28].

Studies about integrating the psychological factors are few but the quality is high. Psychological factors are consistently found to be relevant in the maintenance of persistent pelvic and urogenital pain with current neurobiological understanding of pain. Beliefs about pain contribute to the experience of pain [29] and symptom-related anxiety and central pain amplification may be measurably linked, as in IBS [30]. Central sensitisation has been demonstrated in symptomatic endometriosis [31] and central changes are evident in association with dysmenorrhoea and increasingly recognised as a risk for female pelvic pain [32]. The various mechanisms of CNS facilitation, amplification and failure of inhibition, mean that there is no simple relationship between physical findings, pain experienced and resulting distress and restriction of activities. Diagnoses that assign women's pain to psychological origins, as is common in primary care [33] due to scepticism about the reality or severity of their pain [34], undermines any therapeutic relationship [35]. Division of aetiology into organic vs. psychogenic is unscientific. Pelvic pain and distress may be related [36, 37] in men as well as in women [38]; the same is true of painful bladder and distress [39]. In a large population based study of men, CPPS was associated with prior anxiety disorder [40]. The only systematic review [41] of risk factors for chronic non-cyclical pelvic pain in women included, as well as medical variables: sexual or physical abuse (OR from 1.51 to 3.49); psychological problems such as anxiety (OR: 2.28, 95% CI: 1.41- 3.70) and depression (OR: 2.69, 95% CI: 1.86-3.88); multiple somatic problems (OR: 4.83, 95% CI: 2.50-9.33); and psychosomatic symptoms (OR: 8.01, 95% CI: 5.16-12.44).

Many studies have reported high rates of childhood sexual abuse in adults with persistent pain, particularly in women with pelvic pain [42, 43]. In these studies it is suggested that there is increased frequency of sexual abuse or trauma history, anxiety and depression in women with CPP [44-48]. The only prospective investigation into the relationship between childhood sexual abuse, physical abuse, or neglect, and "medically unexplained pain", including pelvic pain, used court records to compare women with a definite history with matched classmates [26] and concluded that physically and sexually abused individuals were not at risk for increased pain, although women with pain problems as adults were more likely to report earlier sexual or physical abuse or neglect. The correlation between childhood victimisation and pain may concern retrospective explanations for pain; controlling for depression significantly weakens the relationship between childhood abuse and adult pain [49]. Disentangling the influences and inferences requires further prospective studies or careful comparisons [23]. There is some evidence for a specific relationship between rape and CPP (and with fibromyalgia and functional gastrointestinal disorders) [50]; and, recent sexual assault may prompt presentation of pelvic pain [42, 51]. Few studies have been found of sexual or physical abuse in childhood and pelvic pain in men, although it has known adverse effects on health [50, 52]. In the BACH study, it was found that men who reported having experienced sexual, physical, or emotional abuse had increased odds (3.3 compared to 1.7) for symptoms suggestive of CPP. The authors suggested that clinicians may wish to screen for abuse in men presenting with symptoms suggestive of CPP. Conversely, clinicians may wish to inquire about pelvic pain in patients who have experienced abuse [53].

3.1.5.2 *Underlying causes*

The mechanisms that serve as an underlying cause for chronic pelvic pain are:

1. Ongoing acute pain mechanisms [54] (such as those associated with inflammation or infection), which may involve somatic or visceral tissue.
2. Chronic pain mechanisms, which especially involve the CNS [6].
3. Emotional, cognitive, behavioural and sexual responses and mechanisms [55-57].

Symptoms and signs of neuropathic pain appear to be common in CPP patients and assessment of neuropathic pain should be considered in that group of patients. The presence or absence of endometriosis does not seem to change this [58].

Chronic pain mechanisms may include altered resting state neuromotor connectivity, for instance in men with chronic prostatitis/CPPS [59].

Table 3 illustrates some of the differences between the somatic and visceral pain mechanisms. These underlie some of the mechanisms that may produce the classical features of visceral pain; in particular, referred pain and hyperalgesia.

Table 3: Comparison between visceral and somatic pain

	Visceral pain	Somatic pain
Effective painful stimuli	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
Summation	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
Autonomic involvement	Autonomic features (e.g., nausea and sweating) frequently present.	Autonomic features less frequent.
Referred pain	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised but well recognised.
Referred hyperalgesia	Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.	Hyperalgesia tends to be localised.
Innervation	Low density, unmyelinated C fibres and thinly myelinated A δ fibres.	Dense innervation with a wide range of nerve fibres.
Primary afferent physiology	Intensity coding. As stimulation increases, afferent firing increases with an increase in sensation and ultimately pain.	Two fibre coding. Separate fibres for pain and normal sensation.
Silent afferents	50-90% of visceral afferents are silent until the time they are switched on.	These fibres are very important in the central sensitisation process. Silent afferents present, but form a lower percentage.
Central mechanisms	Play an important part in the hyperalgesia, viscerovisceral, visceromuscular and musculovisceral hyperalgesia.	Sensations not normally perceived become perceived and non-noxious sensations become painful. Responsible for the allodynia and hyperalgesia of chronic somatic pain.
Abnormalities of function	Central mechanisms associated with visceral pain may be responsible for organ dysfunction.	Somatic pain associated with somatic dysfunction, e.g., muscle spasm
Central pathways and representation	As well as classical pathways, there is evidence for a separate dorsal horn pathway and central representation.	Classical pain pathways.

Ongoing peripheral pain mechanisms in visceral pain

In most cases of CPP, ongoing tissue trauma, inflammation or infection is absent [60-63]. However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in CPP in a small proportion of cases. For example, out of a large cohort with acute bacterial prostatitis, 10.5% ended up with a state of CPPS [64]. It is for this reason that the early stages of assessment include looking for these pathologies [11]. Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are activated by a nociceptive event, as well as direct activation of the peripheral nociceptor transducers, sensitisation of those transducers may also occur, therefore magnifying the afferent signaling. Afferents that are not normally active may also become activated by the change, that is, there may be activation of the so-called silent afferents. Although these are mechanisms of acute pain, the increased afferent signaling is often a trigger for the chronic pain mechanisms that maintain the perception of pain in the absence of ongoing peripheral pathology (see below) [65, 66].

There are a number of mechanisms by which the peripheral transducers may exhibit an increase in sensibility.

1. Modification of the peripheral tissue, which may result in the transducers being more exposed to peripheral stimulation.
2. There may be an increase in the chemicals that stimulate the receptors of the transducers [67].
3. There are many modifications in the receptors that result in them being more sensitive.

In general, the effect of 1 and 2 is to lower the threshold and the effect of 3 is to increase responsiveness to external stimuli. Some of the chemicals responsible for the above changes may be released from those cells associated with inflammation, but the peripheral nervous system may also release chemicals in the positive and inhibitory loops [68].

Central sensitisation as a mechanism in visceral pain

It is important to appreciate that nociception is the process of transmitting information to centres involved in perception of a stimulus that has the potential to cause tissue damage. Pain is far more complex and involves activation of the nociceptive pathways but also the emotional response. The brain may affect the modulation of pain pathways at the spinal cord level.

Central sensitisation [69] is responsible for a decrease in threshold and an increase in response duration and magnitude of dorsal horn neurons. It is associated with an expansion of the receptive field. As a result, sensitisation increases signaling to the CNS and amplifies what we perceive from a peripheral stimulus. As an example, for cutaneous stimuli, light touch would not normally produce pain, however, when central sensitisation is present, light touch may be perceived as painful (allodynia). In visceral hyperalgesia (so called because the afferents are primarily small fibres), visceral stimuli that are normally sub-threshold and not usually perceived, may be perceived. For instance, with central sensitisation, stimuli that are normally sub-threshold may result in a sensation of fullness and a need to void or to defecate. Non-noxious stimuli may be interpreted as pain and stimuli that are normally noxious may be magnified (true hyperalgesia) with an increased perception of pain. As a consequence, one can see that many of the symptoms of BPS and IBS may be explained by central sensitisation. A similar explanation exists for the muscle pain in FM.

It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain [70]. Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main contenders are the opioids, 5-hydroxytryptamine and noradrenaline.

The autonomic nervous system also plays a role in sensitisation. There is good evidence that damaged afferent fibres may develop a sensitivity to sympathetic stimulation, both at the site of injury and more centrally, particularly in the dorsal horns. In visceral pain, the efferent output of the CNS may be influenced by central changes (again, those changes may be throughout the neuraxis), and such modification of the efferent message may produce significant end-organ dysfunction. These functional abnormalities can have a significant effect on QoL and must be managed as appropriate.

Psychological mechanisms in visceral pain

Psychological processes of emotions, thought and behaviour involve networks rather than distinct centres. Some of these processes are sophisticated and others fundamental in evolutionary terms, and their interaction with pain processing is complex.

Various psychological processes affect pain neuromodulation at a higher level. Inhibiting or facilitating both the nociceptive signal reaching the consciousness and appraisal and interpretation of that signal, will also modulate the response to the nociceptive message and hence the pain experience. Further, descending pathways represent cognitive, emotional and behavioural states at spinal and peripheral levels. Functional magnetic resonance imaging (fMRI) has indicated that the psychological modulation of visceral pain probably involves multiple pathways. For instance, mood and attentional focus probably act through different areas of the brain when involved in reducing pain [71].

This psychological modulation may act to reduce nociception within a rapid time frame but may also result in long-term vulnerability to chronic visceral pain, through long-term potentiation. This involvement of higher centre learning may be at both a conscious and subconscious level, and is clearly significant in the supratentorial neuroprocessing of nociception and pain. Long-term potentiation [72] may occur at any level within the nervous system, so that pathways for specific or combinations of stimuli may become established, resulting in an individual being vulnerable to perceiving sensations that would not normally be experienced as painful.

An important review [23] of CPP in women identifies the notion that women without physical findings to which pain can be causally attributed differ in psychological characteristics from women with physical findings. It argues for better methodology, and for greater use of idiographic methods. In summary, women with pelvic pain often have other 'medically unexplained' symptoms, and current or lifetime anxiety and depression

disorder; they may have a history of physical or sexual abuse in childhood of unclear significance. Studies that invoke 'medically unexplained' or 'psychosomatic' or 'somatoform' disorders are entirely inconsistent with current pain science, ignoring phenomena such as viscerovisceral cross sensitisation in relation to multiple pain sites [73], and interpreting absence of physical findings to indicate psychological origins of the complaint [74, 75]. Some pain problems which affect sexual activity are diagnosed as sexual problems (e.g. 'dyspareunia') when pain is the central problem and not contingent on sexual activity alone [76]. Better integration of sexology and mainstream psychology for pelvic pain in both men and women is needed [77], building on a biopsychosocial formulation [78, 79].

The term psychosomatic symptoms can best be understood as multiple somatic symptoms not associated with or indicative of any serious disease process. Medical and surgical history may also be important [80]. There have been a few studies of maintenance of, or recovery from, pelvic pain in relation to psychological factors of importance in pain. Those that described pelvic pain as medically unexplained or psychosomatic, due to the lack of physical findings, have been discarded, because such a distinction is inconsistent with known pain mechanisms [74].

Understanding the psychological components of pain

Psychological processes of emotions, thought and behaviour involve networks rather than distinct centres, and their interaction with pain processing is complex, producing inhibition and facilitation of signal processing, appraisal, and response. Models that integrate the psychological factors consistently found to be relevant in the maintenance of persistent pelvic and urogenital pain with current neurobiological understanding of pain are few but the quality is high (see 3.1.5.1).

There is no evidence that women with CPP without physical findings are primarily presenting a psychological problem [23]. Anxiety and post-traumatic stress symptoms are common in some women with CPP [33, 81] and with vulvar pain [82], and may account for substantial variance in health status and treatment use. Negative investigative findings do not necessarily resolve women's anxieties about the cause of pain [83, 84] and anxiety often focuses on what might be 'wrong' [85]. Depression may be related to pain in various ways, as described above. Until measures are available that are adequately standardised in patients with pain, anxiety and distress may be best assessed by questions about concerns about the cause of pain, the hope that diagnosis will validate pain, the struggle with unpredictability, and the implications of pain for everyday life [86, 87]. Reference to the studies of the IMMPACT group [88] is recommended for guidance on outcome measures suitable for pain trials.

Stress can modify the nervous system to produce long-term biological changes. These structural changes may be responsible for significant early life and adverse life events which are associated with chronic pain syndromes [26]. The patient should be asked about adverse life events that may produce these biological responses and affect a patient's general psychological well-being [25, 26, 89].

3.1.5.3 Clinical paradigms in visceral pain

Referred pain

Referred pain is frequently observed and its identification is important for diagnosis and treatment. Referral is usually somatic to somatic, or visceral to somatic. However, there is no reason why pain cannot also be perceived within the area of an organ with the nociceptive signal having arisen from a somatic area. Referred pain may occur as a result of several mechanisms but the main theory is one of convergence-projection. In the convergence-projection theory, as an example, afferent fibres from the viscera and the somatic site of referred pain converge onto the same second order projection neurons. The higher centres receiving messages from these projection neurons are unable to separate the two possible sites from the origin of the nociceptive signal [61, 65, 90].

Hyperalgesia refers to an increased sensitivity to normally painful stimuli. In patients that have passed a renal stone, somatic muscle hyperalgesia is frequently present, even a year after expulsion of the stone. Pain to non-painful stimuli (allodynia) may also be present in certain individuals. Somatic tissue hyperaesthesia is associated with urinary and biliary colic, IBS, endometriosis, dysmenorrhoea, and recurrent bladder infections. Vulvar pain syndromes are examples of cutaneous allodynia that, in certain cases, may be associated with visceral pain syndromes, such as BPS. Referred pain with hyperalgesia is thought to be due to central sensitisation of the converging viscerosomatic neurons. Central sensitisation also stimulates efferent activity that could explain the trophic changes that are often found in the somatic tissues.

Muscles and pelvic pain

In the urogenital pain syndromes, muscle tenderness and trigger points may be implicated as a source of pain.

Central mechanisms are of great importance in the pathogenesis of this muscle hyperalgesia. The muscles involved may be a part of the spinal, abdominal or pelvic complex of muscles. It is not unknown for adjacent muscles of the lower limbs and the thorax to become involved. Pain may be localised to the trigger points but it is more often associated with classical referral patterns. As well as trigger points, inflammation of the attachments to the bones (enthesitis) and of the bursa (bursitis) may be found [91]. Certain postures affect the different muscles in different ways, and as a consequence, may exacerbate or reduce the pain. Stress has been implicated as both an initiator of pelvic myalgia and as a maintenance factor. As a result, negative sexual encounters may also have a precipitating effect [23].

Visceral hyperalgesia

The increased perception of stimuli in the viscera is known as visceral hyperalgesia, and the underlying mechanisms are thought to be responsible for IBS, BPS and dysmenorrhoea. The mechanisms involved are often acute afferent input (e.g., due to infection) followed by long-term central sensitisation. Viscero-visceral hyperalgesia is thought to be due to two or more organs with converging sensory projections and central sensitisation. For instance, overlap of bladder and uterine afferents or uterine and colon afferents.

3.2 Pelvic Pain

3.2.1 Incidence

No adequate data on incidence were found.

3.2.2 Prevalence

3.2.2.1 Prostate Pain syndrome

There is only limited information on the true prevalence of PPS in the population. As a result of significant overlap of symptoms with other conditions (e.g. benign prostatic enlargement and BPS), purely symptom-based case definitions may not reflect the true prevalence of PPS [92, 93]. In the literature, population-based prevalence of prostatitis symptoms ranges from 1 - 14.2% [94, 95]. The risk of prostatitis increases with age (men aged 50-59 years have a 3.1-fold greater risk than those aged 20-39 years).

3.2.2.2 Bladder Pain syndrome

Reports of BPS prevalence have varied greatly, along with the diagnostic criteria and populations studied. Recent reports range from 0.06% to 30% [96-105]. There is a female predominance of about 10:1 [102, 106-108] but possibly no difference in race or ethnicity [92, 109, 110]. The relative proportions of classic and non-lesion disease are unclear. Incidence in studies has ranged from 5 to 50% [111-115]. There is increasing evidence that children under 18 may also be affected, although prevalence figures are low; therefore, BPS cannot be excluded on the basis of age [116].

3.2.2.3 Sexual pain syndrome

In the 1980s an association between CPP and sexual dysfunction was postulated. In two reviews the relationship between PPS and health status, with influence on sexual activity, was addressed [117, 118]. In a Chinese study of men with CPP 1,768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction (ED) is the most investigated sexual dysfunction in PPS patients. The reported prevalence of ED ranges from 15.1% to 48%, varying with evaluation tools and populations [119, 120]. Erectile dysfunction was prevalent in 27.4% of Italian men aged 25-50 [121], 15.2% among Turkish men (significantly higher than in the control group) [122] and 43% among Finnish men with PPS [123]. The prevalence of ED was found to be higher in young men with PPS than in the general population. According to other studies men with pelvic pain had a higher chance of suffering from ED [124, 125]. Recently, a significant correlation between "chronic prostatitis", CPP symptoms (measured by NIH-CPSI) and ED (measured by IIEF) was confirmed [126], while other studies using the same questionnaires were not able to confirm such a correlation [79, 127]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [119, 120, 128, 129].

In community-based studies in the UK [130], New Zealand [131] and Australia [132], a substantially larger proportion of the women with CPP reported dyspareunia (varying between 29% and 42%) than women without CPP (varying between 11% and 14%). Only a few studies have investigated sexual problems within clinical populations [133]. Another study showed that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) were significantly lower in women with CPP than in women without CPP [133]. In line with the results of community based studies, patients with CPP reported more sexual problems such as dyspareunia, problems with desire or arousal and lubrication than women without CPP [133, 135, 136]. One study of patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems [137].

3.2.2.4 *Myofascial pain syndromes*

The relationship between muscular dysfunction (especially over-activity) and pelvic pain has been found in several studies [138]. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles [139]. The vast majority (92.2%) of men visiting a tertiary centre for pelvic pain had dysfunction of the pelvic floor muscles. This finding was true regardless of evidence of inflammation (prostatitis or cystitis) [140]. This relationship has been found in chronic prostatitis [141], BPS [142] and vulvar pain [143]. Dysfunction of the pelvic floor directly affects function of the pelvic viscera and vice versa. Both systems can act as the primary signal to the spinal cord, with a cascade of reactions ascending to the CNS as a result. The muscle itself ends up with a diminished length, leading to restrictions even when it is in a relaxed state.

3.2.3 **Influence on QoL**

Data on the influence on QoL will be included in the next version of the guidelines.

3.2.4 **Costs**

No adequate data on costs were found.

3.2.5 **Risk factors and underlying causes**

The risk factors are unspecific for most of the pain syndromes in the pelvic area. They are described in 3.1.5.1. The underlying causes, including the mechanisms are described here for the different clinical pain syndromes.

3.2.5.1 *Prostate Pain Syndrome*

Pain is the main symptom in PPS. As a common feature of chronic pain syndromes, no single aetiological explanation has been found. One explanation [144] is that the condition probably occurs in susceptible men exposed to one or more initiating factors, which may be single, repetitive or continuous. Several of these potential initiating factors have been proposed, including infectious, genetic, anatomical, neuromuscular, endocrine, immune (including autoimmune), or psychological mechanisms. These factors may then lead to a peripheral self-perpetuating immunological, inflammatory state and/or neurogenic injury, creating acute and then chronic pain. Based on the peripheral and the central nervous system, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state [144]. This could also explain why tissue damage is not usually found in PPS. There is growing evidence for a neuropathic origin and association with CNS changes of pain in PPS and anxiety appears to be a risk factor for its development [40].

3.2.5.2 *Bladder Pain syndrome*

An initial unidentified insult to the bladder, leading to urothelial damage, neurogenic inflammation and pain is thought to be the cause of BPS. However, BPS might be a local manifestation of a systemic disorder. No infection has as yet been implicated. Nevertheless, urinary infection is significantly more frequent during childhood and adolescence, in patients with BPS in adulthood [145]. Experimental induction of CPP by O-antigen deficient bacterial strains reinstates the bacterial hypothesis [146]. Pancystitis, with associated perineural inflammatory infiltrates, and mast cell count increase is an essential part of BPS type 3 C [147], but is scant in non-lesion BPS [26, 71, 148, 149]. Cystoscopic and biopsy findings in both lesion and non-lesion BPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer, which might expose submucosal structures to noxious urine components [150-157] and a consequent cytotoxic effect [158, 159]. Basic and clinical studies indicate that autonomic dysfunction with sympathetic predominance may be implicated in BPS [160, 161].

An association has been reported between BPS and non-bladder syndromes such as FM, chronic fatigue syndrome (CFS), IBS, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma and systemic lupus erythematosus [162-168].

Risk of BPS correlates with a number of non-bladder syndromes in each patient [169]. Recent work showing non-lesion BPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than BPS type 3C patients, emphasises the need for subtyping [170].

3.2.5.3 *Scrotal Pain Syndrome*

Often scrotal pain is not associated with any specific pathology. Pain is perceived in the testes, epididymis, or the vas deferens. The ilioinguinal, genitofemoral and the pudendal nerves innervate the scrotum [171]. Any pathology or intervention at the origin or along the course of the nerves may result in pain perceived in the scrotum [172].

Two special forms of scrotal pain syndrome can be described. The first one is the post-vasectomy scrotal pain syndrome which occurs following vasectomy. The mechanisms are poorly understood and it is for that reason considered a special form of scrotal pain syndrome. Incidence of post-vasectomy pain is 2-20% among all men who have undergone a vasectomy [173]. In men with post-vasectomy pain, 2-6% have a VAS score > 5 [174]. In a large cohort study of 625 men, the likelihood of scrotal pain after six months was 14.7%. The mean pain severity on a VAS score was 3.4/10. In the pain group, 0.9% had quite severe pain, noticeably affecting their daily life. In this cohort, different techniques were used to perform the vasectomy. The risk of post-vasectomy pain was significantly lower in the no-scalpel vasectomy group (11.7% vs. the scalpel group 18.8%) [175].

The second special form of scrotal pain is post-inguinal hernia repair pain. It is seen as a complication of hernia repair, but in trials it is seldom reported or it is put under the term chronic pain (not specified). In studies that have explicitly mentioned scrotal pain, there was a difference in incidence between laparoscopic and open hernia repair. In almost all studies, the frequency of scrotal pain was significantly higher in the laparoscopic than in the open group [172, 176]. In one particular study, there was no difference at one year but after five years, the open group had far fewer patients with scrotal pain [177].

3.2.5.4 Urethral Pain Syndrome

Some mechanisms for the development of urethral pain syndrome have been proposed. The intimate relation of the urethra with the bladder (both covered with urothelium) suggests that urethral pain syndrome may be a form of BPS. Mechanisms thought to be basic for BPS may also apply to the urethra. This means that the specific testing with potassium has been used to support the theory of epithelial leakage [178, 179]. Another possible mechanism is neuropathic hypersensitivity following urinary tract infection [180]. The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multi-parity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis [181].

3.2.5.5 Vaginal and vulvar pain syndromes

Pain in the vagina or the female external genital organs is often due to infection or trauma, as a consequence of childbirth or surgery. Pain is usually a precedent to dyspareunia. When the pain persists for more than six months, it can be diagnosed as vulvar pain syndrome previously known as “vulvodynia” or “chronic vaginal pain” with no known cause. It is still a poorly understood condition, and thus difficult to treat.

There are two main subtypes of vulvar pain syndrome: generalised, where the pain occurs in different areas of the vulva at different times; and focal, where the pain is at the entrance of the vagina. In generalised vulvar pain syndrome, the pain may be constant or occur occasionally, but touch or pressure does not initiate it, although it may make the pain worse. In focal vulvar pain syndrome, the pain is described as a burning sensation that comes on only after touch or pressure, such as during intercourse.

The possible causes of vulvar pain syndrome are many and include:

- History of sexual abuse;
- History of chronic antibiotic use;
- Hypersensitivity to yeast infections, allergies to chemicals or other substances;
- Abnormal inflammatory response (genetic and non-genetic) to infection and trauma;
- Nerve or muscle injury or irritation;
- Hormonal changes.

3.2.5.6 Associated conditions in pelvic pain syndromes

Nerve damage

Spinal pathology and any pathology along the course of the nerve involved may result in neuropathic pain in the distribution of these nerves. Neoplastic disease, infection and trauma, surgical incisions and post-operative scarring may result in nerve injury [182].

Pudendal neuralgia is the most often mentioned form of nerve damage in the literature. Anatomical variations may pre-dispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) [183, 184].

The pudendal nerve may be damaged at the level of:

1. The piriformis muscle. For example, as part of a piriformis syndrome: in some cases, the nerve may pass through the muscle and hence be trapped; or in other cases, muscle hypertrophy or spasm is implicated.

2. The sacrospinal/sacrospinous ligaments, possibly accounting for 42% of cases.
3. Within Alcock's canal (medial to the obturator internus muscle, within the fascia of the muscle), possibly accounting for 26% of cases.
4. Multiple levels in 17% of cases.

The site of injury determines the site of perceived pain and the nature of associated symptoms (e.g., the more distal the damage, the less likely the anal region will be involved).

The clinical presentation depends on different factors. There is a wide age range, as one would expect with a condition that has so many potential causes. There is a suggestion that, the younger the patient, the better the prognosis. Essentially, the sooner the diagnosis is made, as with any compression nerve injury, the better the prognosis, and older patients may have a more protracted problem [185-187]. Six out of ten cases are observed in women. Some special situations can be listed:

- In orthopaedic hip surgery, pressure from the positioning of the patient, where the perineum is placed hard against the brace, can result in pudendal nerve damage [188, 189]. The surgery itself may also directly damage the nerve. Pelvic surgery such as sacrospinous colpopexy is clearly associated with pudendal nerve damage in some cases [190, 191]. In many types of surgery, including colorectal, urological and gynaecological, pudendal nerve injury may be implicated.
- Fractures of the sacrum or pelvis may result in pudendal nerve/root damage and pain. Falls and trauma to the gluteal region may also produce pudendal nerve damage if associated with significant tissue injury or prolonged pressure.
- Tumours in the pre-sacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer [192].
- The pudendal neuralgia of birth trauma is thought to resolve in most cases over a period of months. However, rarely, it appears to continue as painful neuropathy. Multiple pregnancies and births may predispose to stretch neuropathy in later life. This is more difficult to be certain about [193].
- Child birth and repeated abdominal straining associated with chronic constipation [194] are thought to pre-dispose elderly women to post-menopausal pelvic floor descent and stretching of the pudendal nerve with associated pain. Changes in the hormone status may also be a factor. In the Urogenital Pain Management Centre, the commonest associations with pudendal neuralgia appear to be: history of pelvic surgery; prolonged sitting (especially young men working with computer technology); and post-menopausal older women.

Sexual dysfunction

Chronic pelvic pain is a clinical condition that results from the complex interactions of physiological and psychological factors and has a direct impact on the social, marital and professional lives of men and women.

Men

Chronic pain and its treatment can impair our ability to express sexuality. In a study in England, 73% of patients with chronic pain had some degree of sexual problems as result of the pain [137]. These problems can occur because of several factors. Psychological factors like decrease in self-esteem, depression and anxiety can contribute to loss of libido. Physiological factors like fatigue, nausea and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin re-uptake inhibitors (SSRIs) can also decrease libido [195] and delay ejaculation. The number of studies on the effects of CPP on sexual function is limited. Sexual dysfunction is often ignored because of a lack of standardised measurements. At present, the most commonly used tool is the International Index of Erectile Function (IIEF) questionnaire [127].

The presence of pelvic pain may increase the risk for ED independent of age [196-198]. On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation [118]. Although mental distress and impaired QoL related to illness could contribute to sexual dysfunction observed in patients with PPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms suggestive of a more severe inflammatory condition [129]. These arguments are important for the understanding of the close relationship between CPP symptoms, disturbed sexuality, impact on QoL, and psychological implications including depression [117-120, 199]. Sexual dysfunction heightens anger, frustration and depression, all of which place a strain on the patients' relationships. The female partners of men with sexual dysfunction and depression often present with similar symptoms including pain upon intercourse and depressive symptoms. Men with CPP have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal thinking [117, 197]. PPS patients reported greater sexual and relationship problems [117, 197, 200]. On the other hand, it was found that men with PPS did not report significantly decreased sexual satisfaction compared to controls [201]. There is consensus that therapeutic strategies reducing symptoms of pelvic pain are of relevance in relation to changes

in sexual function. Also intimacy and having sex can yield positive experiences that will reduce the pain. The CNS plays an important role in this mechanism.

Women

Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions [131, 202-204]. It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect women's sexuality. Women with CPP reported significantly more pain, depression, and anxiety symptoms and were physically more impaired than women in the control group. In comparison with controls, women with CPP reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [205]. In one study of CPP patients' feelings and beliefs about their pain or illness, 40 out of 64 participants cited sexual dysfunction as one of the main problems the illness had caused, making it the most frequent complaint [206]. Patients with CPP reported more sexual problems than women with any other type of chronic pain problem [207]. The quality of intimate relationships is closely connected with sexual function [208]. Satisfaction with sexual relationships appears to be associated with higher marital functioning [209]. In addition sexual dissatisfaction is related to sexual dysfunction. When one partner suffers from chronic pain, the ability of both partners to cope with the pain and the extent to which partners are supportive of the chronic pain sufferer have been found to be a predictor of sexual functioning [209].

Approximately two-thirds of patients in another study reported reduced frequency in their sexual relations as a result of CPP [210]. One study demonstrated that CPP patients reported worse sexual function with regard to desire, arousal, lubrication, orgasm, satisfaction, and more frequent and severe pain with vaginal penetration than women without CPP [211]. In an interview with 50 chronic pain sufferers and their spouses, 78% of the pain sufferers and 84% of partners described deterioration, including cessation of their sex life [196]. In a study in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain [137]. The Female Sexual Function Index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. Using the FSFI, women with CPP reported worse sexual function in all subscales and total score than women without CPP. The largest differences between women with CPP and without CPP were seen for the domains of pain and arousal. The total score and the subscales of the FSFI had high levels of internal consistency and test-retest reliability when assessed in a sample of women with CPP. The FSFI also showed good ability to discriminate between women with and without CPP [211].

Myofascial pain

Chronic pelvic pain can simply be a form of myalgia, due to the muscles being used in an abnormal way, in this case, the pelvic floor muscles. Studies in the field of chronic prostatitis support the idea that patients with CPP have more muscle spasm and increased muscle tone and report pain when the pelvic floor muscles are palpated [212]. Muscle relaxation can diminish spasm and pain [213]. Repeated or chronic muscular overload can activate trigger points in the muscle. A report from the Chronic Prostatitis Cohort Study showed that 51% of patients with prostatitis and only 7% of controls had any muscle tenderness. Tenderness in the pelvic floor muscles was only found in the CPP group [141].

In 1999, the first ideas about the neurological aspects of the pelvic floor muscles in relation to CPP were published. The probability of CNS breakdown in the regulation of pelvic floor function was suggested as a mechanism for development of CPP. Of the patients presenting with pelvic pain, 88% had poor to absent pelvic floor function [140]. Basic studies on the role of neurogenic inflammation have also elucidated some important phenomena. Irritation of the prostate, bladder and pelvic floor muscles results in expression of C-fos-positive cells in the CNS. There appears to be convergence of afferent information onto central pathways. Once the central changes have become established, they become independent of the peripheral input that initiated them [214].

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyperirritable spots within a taut band. Other criteria for trigger points are: recognition of the pain as 'familiar', and pain on stretching the muscle. Apart from pain, trigger points prevent full lengthening of the muscle, thereby restricting the range of movement. Pain as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Positions and movements in which the shortened muscle is stretched are painful. Patients know which activities and postures influence pain. Trigger points can be located within the pelvic floor muscles and in adjacent muscles such as the abdominal, gluteal and iliopsoas muscles. Pain is aggravated by pressure on the trigger point (e.g., pain related to sexual intercourse). Pain also worsens after sustained or repeated contractions (e.g., pain related to voiding or defecation).

3.3 Abdominal aspects of pelvic pain

3.3.1 Incidence

Epidemiological data on IBS and CPP are scarce. CPP has been shown to be one of the most common functional disorders in women of reproductive age. The monthly incidence rate of CPP published by Zondervan was 1.58/1000 [215].

3.3.2 Prevalence

Using a vague definition of continuous or episodic pain situated below the umbilicus over six months, one study reported that CPP was one of the most common diagnosis in primary care units in Great Britain [215]. The monthly prevalence rate of CPP in this study was 21.5/1,000, with an annual prevalence of 38.3/1,000. They increase significantly with older age and vary significantly between regions in the UK. The overall prevalence of anorectal pain in a sample of USA householders was 6.6% and was more common in women [216]. IBS is associated with common gynaecologic problems (endometriosis, dyspareunia, and dysmenorrhoea) [217]. 50% of women who presented with abdominal pain to the gynaecologic clinic or were scheduled for laparoscopy due to CPP had symptoms of IBS [218]. In a survey from Olmsted county 20% of women reported CPP and 40% of those met criteria for IBS [16]. This overlap of CPP and IBS was associated with an increased incidence of somatisation. Not gynaecological surgical procedures but only psychosocial variables predict pain development without a different incidence of IBS in a prospective and controlled study [219]. Clinical features of pelvic floor dysfunction, gynaecological and psychological features are related to disordered anorectal function in IBS patients but do not predict physiological anorectal testing.

3.3.3 Influence on QOL

There is little known on health related quality of life (HRQoL) in patients with CPP and a need to develop validated disease specific HRQoL instruments for CPP in addition to sound measurement properties. More data are available in patients with IBS treated at referral centres who have comparable HRQoL scores as patients with other common disorders such as diabetes, end-stage renal disease, and inflammatory bowel disease [220]. Subgroups of IBS with predominance of diarrhoea or constipation show no difference in HRQoL. Multi-variate analysis shows that HRQoL in patients with IBS is affected by sex and psychological conditions.

3.3.4 Costs

Costs combine direct health-care costs and societal costs (productivity loss) such as under-performance and absenteeism from work. The annual costs to society can be calculated by using the average population earnings. In Germany direct care costs are estimated at €791 and societal costs €995 per patient with IBS per year which may be comparable to patients with CPP [221].

3.3.5 Risk factors & underlying causes

Risk factors are covered in Section 3.1.5.

3.4 Summary of evidence and recommendations: CPP and mechanisms

Summary of evidence	LE
CPP mechanisms are well defined and involve mechanisms of neuroplasticity and neuropathic pain.	2
The mechanisms of neuroplasticity and neuropathic pain result in increased perception of afferent stimuli which may produce abnormal sensations as well as pain.	1
End-organ function can also be altered by the mechanisms of neuroplasticity so that symptoms of function can also occur.	1
The diagnosis of a CPPS as a pain syndrome is essential as it encourages a holistic approach to management with multi-specialty and multi-disciplinary care.	2

Recommendations	GR
All of those involved in the management of Chronic Pelvic Pain (CPP) should have knowledge of peripheral and central pain mechanisms.	A
The early assessment of patients with CPP should involve: <ul style="list-style-type: none"> • investigations aimed at specific disease-associated pelvic pain; • assessment of functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation. 	A
CPPS patients should be managed in a multi-specialty and multi-disciplinary environment with consideration of all their symptoms.	A

4. DIAGNOSTIC EVALUATION

4.1 General Evaluation

4.1.1 History

History is very important for the evaluation of patients with CPP. Pain syndromes are symptomatic diagnoses, which are derived from a history of pain perceived in the region of the pelvis, and absence of other pathology, for a minimum of three out of the past six months. This implies that specific disease-associated pelvic pain caused by bacterial infection, cancer, drug-induced pathology (e.g. ketamine use) [222], primary anatomical or functional disease of the pelvic organs, and neurogenic disease must be ruled out.

4.1.1.1 Anxiety, depression, and overall function

Distress is best understood in the context of pain and of the meaning of pain to the individual and is best assessed ideographically rather than normatively. Almost all diagnostic measures and standardised instruments of anxiety and depression are designed for people without significant physical problems, so are hard to interpret in CPP [223-225].

Anxiety about pain often refers to fears of missed pathology (particularly cancer) as the cause of pain [29], or to uncertainties about treatment and prognosis. These can drive healthcare seeking behaviour [20]. The question: "What do you believe or fear is the cause of your pain?" has been suggested [226]. Anxiety may also concern urinary urgency and frequency as a possible problem in social settings.

Depression or depressed mood are common in chronic pain [227] e.g. often related to losses consequent to chronic pain (work, leisure activities, social relationships, etc.). Because of the lack of suitable assessment instruments, it is better to ask a simple question such as "How does the pain affect you emotionally?" If the answer gives cause for concern about the patient's emotional state, further assessment should be undertaken by an appropriately qualified colleague.

Most measures of restricted function are designed primarily for musculoskeletal pain and may emphasise mobility problems rather than the difficulties of the individual with pelvic or urogenital pain. A promising specific measure, UPOINT, was introduced and in a later version the sexological aspects were added [228]. However, it may under-assess relevant psychological variables [38]. Generic QoL measures are helpful. If such an instrument is not already used in the clinic, the Brief Pain Inventory [229] provides a broad and economical assessment of interference of pain with various aspects of life in multiple languages. (For further suggested instruments see [230]). In a study, more pain, pain-contingent rest, and urinary symptoms were associated with poorer function [57].

4.1.1.2 Urological aspects

Pain may be associated with urological symptoms. A detailed history of lower urinary tract functions should be taken. Dysfunctions of the lower urinary tract may exacerbate symptoms, as pain may interfere with the function of the lower urinary tract. Micturition in all its aspects should be addressed. Special attention should be paid to the influence of micturition on the experience of pain.

Prostate pain syndrome

Prostate pain syndrome is diagnosed from a history of pain perceived in the region of the prostate (convincingly reproduced by prostate palpation), and absence of other lower urinary tract pathology, for a minimum of three out of the past six months. As mentioned above, specific disease-associated pelvic pain must be ruled out.

A thorough history is an important first step in the evaluation of PPS. It should include type of pain and localisation. Pain is often reported in other pelvic areas outside the prostate such as perineum, rectum, penis, testicles and abdomen [49]. In addition, associated lower urinary tract symptoms, sexual function, psychological, social and economic factors should be addressed. Determination of the severity of disease, its progression and treatment response can be assessed only by means of a validated symptom-scoring instrument (see section 4.2.3). These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients in urological practice.

Bladder pain syndrome

Bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 4) [11].

The nature of pain is key to disease definition:

1. pain, pressure or discomfort perceived to be related to the bladder, increasing with increasing bladder content;
2. located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum;
3. relieved by voiding but soon returns [231-235];
4. aggravated by food or drink [235].

Bladder pain syndrome type 3 can lead to a small capacity fibrotic bladder with or without upper urinary tract outflow obstruction.

4.1.1.3 *Gynaecological aspects*

A detailed medical history outlining the nature, frequency and site of pain; its relationship to precipitating factors and the menstrual cycle, may help define the aetiology. A menstrual and sexual history, including a history of sexually transmitted diseases, vaginal discharge, as well as previous sexual trauma is mandatory as well as up to date cervical cancer screening.

4.1.1.4 *Gastrointestinal aspects*

The predominant symptoms that patients are interviewed about are discomfort or pain in relation to their bowel habits, daily activities, and eating. A precise history of dysfunctional voiding or defecation should be asked, ideally applying symptom questionnaires for urinary and anorectal symptoms (e.g., Rome III criteria for anorectal pain). Excessive straining at most defecations, anal digitations in dyssynergic defecation, and a sensation of anal blockage may be found in patients with chronic anal pain. History of anxiety and depression with impaired QoL is often encountered in anorectal functional disorders and should be evaluated.

Diagnostic criteria for chronic anal pain syndrome (chronic proctalgia) according to the Rome III criteria are as follows and must include all of the following: chronic or recurrent rectal pain or aching, episodes last at least 20 min and exclusion of other causes of rectal pain such as ischaemia, inflammatory bowel disease, cryptitis, intramuscular abscess and fissure, haemorrhoids, prostatitis, and coccygodynia. These criteria should be fulfilled for the past three months with symptom onset at least six months before diagnosis [236].

The chronic anal pain syndrome includes the above diagnostic criteria and exhibits exquisite tenderness during posterior traction on the puborectalis muscle (previously called “ Levator Ani Syndrome”). Pathophysiology of pain is thought to be due to overactivity of the pelvic floor muscles.

Intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be fulfilled for three months: recurrent episodes of pain localised to the anus or lower rectum, episodes last from several seconds to minutes and there is no anorectal pain between episodes. Stressful life events or anxiety may precede the onset of the intermittent chronic anal pain syndrome. The attacks may last from a few seconds to as long as 30 min. The pain may be cramping, aching or stabbing and may become unbearable. However, most patients do not report it to their physicians and pain attacks occur less than five times a year in 51% of patients.

4.1.1.5 *Peripheral nerve aspects*

A proportion of patients will be able to relate the onset of pain to an acute event such as surgery, sepsis or trauma, and occasionally, cycling for a prolonged period. Chronic injury is more frequent, such as associated with sitting for prolonged periods over time. Many will be idiopathic.

The pain is classically perceived in the perineum from anus to clitoris/penis. However, less-specific pain distribution may occur, and this may be due to anatomical variation, involvement of branches of the nerve rather than the main nerve, CNS central sensitisation, and consequently, the involvement of other organs and systems in a regional pain syndrome. Other nerves in the vicinity may also be involved, for example, inferior cluneal nerve and perineal branches of the posterior femoral cutaneous nerve. The musculoskeletal system may become involved, confusing the pain picture as aches and pain developing in the muscles due to immobility and disability, possibly magnified by the CNS changes.

Burning is the most predominant adjective used to describe the pain. Crushing and electric may also be used, indicating the two components - a constant pain often associated with acute sharp episodes. Many patients may have the feeling of a swelling or foreign body in the rectum or perineum, often described as a golf or tennis ball. The term pain has different meanings to patients and some would rather use the term discomfort or numbness.

Aggravating factors include any cause of pressure being applied, either directly to the nerve or indirectly to other tissue, resulting in pudendal traction. Allodynia is pain on light touch due to involvement of the CNS, and may make sexual contact and the wearing of clothes difficult. These patients often remain standing, and as a consequence, develop a wide range of other aches and pains. Soft seats are often less well-tolerated, whereas sitting on a toilet seat is said to be much better tolerated. If unilateral, sitting on one buttock is common. The pain may be exacerbated by bowel or bladder evacuation.

Pudendal nerve damage may be associated with a range of sensory phenomena. In the distribution of the nerve itself, as well as unprovoked pain; the patient may have paraesthesia (pins and needles); dysaesthesia (unpleasant sensory perceptions usually but not necessarily secondary to provocation, such as the sensation of running cold water); allodynia (pain on light touch); or hyperalgesia (increased pain perception following a painful stimulus, including hot and cold stimuli). Similar sensory abnormalities may be found outside of the area innervated by the damaged nerve, particularly for visceral and muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dyspareunia, but also irritation and pain associated with clothes brushing the skin. There may also be a lack of sensation and pain may occur in the presence of numbness. Visceral hypersensitivity may result in an urge to defecate or urinate. This is usually associated with voiding frequency, with small amounts of urine being passed. Pain on visceral filling may occur. Anal pain and loss of motor control may result in poor bowel activity, with constipation and/or incontinence. Ejaculation and orgasm may also be painful or reduced.

Many of those suffering from pudendal neuralgia complain of fatigue and generalised muscle cramps, weakness and pain. Being unable to sit is a major disability, and over time, patients struggle to stand and they often become bedbound. The immobility produces generalised muscle wasting, and minimal activity hurts. As a consequence of the widespread pain and disability, patients often have emotional problems, and in particular, depression. Patients with CPP are also often anxious and have the tendency to catastrophise. Depression, catastrophising and disability are all poor prognostic markers. Cutaneous colour may change due to changes in innervation but also because of neurogenic oedema. The patient may describe the area as swollen due to this oedema, but also due to the lack of afferent perception.

4.1.1.6 *Myofascial aspects*

When taking a history from a patient with pelvic pain, it is important to address the function of all the organs in the pelvic area. The following items certainly should be addressed: lower urinary tract function, anorectal function, sexual function, gynaecological items, presence of pain and psycho-social aspects. One cannot state that there is a pelvic floor dysfunction based only on the history. But there is a suspicion of pelvic floor muscle dysfunction when two or more pelvic organs show dysfunction, for instance a combination of micturition and defecation problems.

4.1.2 **Physical Evaluation**

The clinical examination often serves to confirm or refute the initial impressions gained from a good history. The examination should be aimed at specific questions where the outcome of the examination may change management. Prior to an examination, best practice requires the medical practitioner to explain what will happen and what the aims of the examination are to the patient. Consent to the examination should occur during that discussion and should cover an explanation around the aim to maintain modesty as appropriate and, if necessary, why there is a need for rectal and/or vaginal examination. Finally, the risk of exacerbating the pain should form a part of that request. A record of the discussion should be noted. The possibility of the presence of a chaperone should be discussed with the patient. As well as a local examination, a general musculoskeletal and neurological examination should be considered an integral part of the assessment and undertaken if appropriate. Following the examination, it is good practice to ask the patient if they had any concerns relating to the conduct of the examination and that discussion should be noted.

There is no specific diagnostic test for CPPS, therefore, procedures are on the one hand directed towards identification and exclusion of specific diseases associated with pelvic pain, and on the other hand may be used for phenotypic description. Abdominal and pelvic examination to exclude gross pelvic pathology, as well as to demonstrate the site of tenderness is essential. Abnormalities in muscle function should also be sought. Examination of the external genitalia is a part of the evaluation. In patients with scrotal pain, gentle palpation of each component of the scrotum is performed to search for masses and painful spots. The penis and urethra may be palpated in a similar way. Many authors recommend that one should assess cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3), and the degree of tenderness should be recorded. The bulbocavernosus reflex in the male may also provide useful information concerning the

Pain assessment ratings are not independent of cognitive and emotional variables [57]. Target outcomes of pain severity, distress and disability co-vary only partly, and improvement in one does not necessarily imply improvement in the others. When the primary outcome is pain its meaning should be anchored in discussion of clinically important difference [239].

Prostate pain syndrome

Reliable, valid indices of symptoms and QoL are the NIH-CPSI [240] and the International Prostate Symptom Score (I-PSS) [241].

Bladder pain syndrome

Symptom scores may help to assess the patient and act as outcome measures. The O'Leary-Sant Symptom Index, also known as the Interstitial Cystitis Symptom Index (ICSI) was validated in a large study [242].

Gastrointestinal questionnaire

The functional anorectal pain disorders (anorectal pelvic pain) are defined and characterised by duration, frequency, and quality of pain. More complex questionnaires are used in the setting of IBS. The validated IBS-Symptom Severity Scale (IBS-SSS) includes the broadest measurement of pain-related aspects [243, 244]. However, as different instruments measure different endpoints of chronic abdominal pain in IBS, a comparison of published studies is often impossible.

Sexual function assessment

In males most frequent effects on sexual function are erectile dysfunction and premature ejaculation. These can be evaluated by proper questionnaires namely IIEF (international index of erectile function) and PEDT (premature ejaculation diagnostic tool). In comparison with controls, women with CPP reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [205]. The female sexual function index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. The corresponding evidence in men is lacking.

4.2.2 Focused myofascial evaluation

Pelvic floor muscle testing can be done by the medical doctor but a consultation of the pelvic floor by a physiotherapist is a good alternative. A vaginal or rectal examination is performed to assess the function of the pelvic floor muscles, according to the International Continence Society (ICS) report. This assessment has been tested and shows satisfactory face validity and intra-observer reliability. It can therefore be considered suitable for use in clinical practice [245]. Rectal examination is a good way to test the pelvic floor function in men [246]. There is a growing number of reports on the use of ultrasound (US) in establishing the function of the pelvic floor muscles. The exact place in the diagnostic setting needs to be addressed in the future [247]. In a cohort study of 72 men with CPP, the relationship between the locations of the trigger point and the referred pain was examined. Ninety percent of the patients showed tenderness in the puborectalis muscle and 55% in the abdominal wall muscles. Of the patients in whom trigger points were found in the puborectalis, 93% reported pain in the penis and 57% in the suprapubic region. Patients with trigger points in the abdominal muscles reported pain in the penis (74%), perineum (65%) and rectum (46%) [248].

4.2.3 Neurological

Injections

An injection of local anaesthetic and steroid at the sight of nerve injury may be diagnostic. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [249-259]. Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, computed tomography (CT) guidance, or the use of US. Ultrasound avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block. Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed.

Electrophysiological studies

These may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernosus reflex [260-264]. However, for an abnormality to be detected, significant nerve damage is probably necessary. Pain may be associated with limited nerve damage, therefore, these investigations are often normal.

4.2.4 **Imaging**

Ancillary studies should be performed according to appropriate guidelines for exclusion of diseases with known aetiology presenting with symptoms identical to those of CPP. Once the latter diagnosis is established studies can be useful to assess functional abnormalities and phenotype conditions such as BPS, and chronic anal pain syndrome.

Ultrasound

Has limited value but may reassure patients. However, over-investigating may be detrimental.

MRI

Magnetic resonance neurography has been increasingly used in specialised centres for the diagnosis of the location (proximal versus peripheral) and degree (total versus partial) of nerve injury in the peripheral nervous system, earlier and with higher specificity than conduction studies.

MR defecating proctogram

Magnetic resonance imaging in conjunction with MR defecography has become the most valuable imaging technique to assess anorectal function dynamically. MRI studies outline simultaneously the anatomy of the pelvic floor and visualise different structural and functional pathologies, by applying dynamic sequences after filling of the rectum with a viscous contrast medium (e.g., US gel). The following pathologies can be visualised: pelvic floor descent, an abnormal anorectal angle while squeezing and straining, rectal intussusception, rectocele, enterocele and cystocele. However, limitations of MR defecography are the left lateral position and the limited space for the patient, which may reduce the ability to strain and thereby reduce the sensitivity of the method, underestimating the size of entero- and rectoceles as well as the amount of intussusception.

Functional neuroimaging (fMRI)

Functional neuroimaging (fMRI, functional magnetic resonance imaging) is currently being re-evaluated as a research tool and some groups have raised issues around over interpretation [265]. With regards to pain, fMRI findings may represent a pain matrix or may represent non-specific threat processing [266]. Currently this panel cannot recommend fMRI as a clinical tool.

4.2.5 **Laboratory Tests**

Microbiology tests

Prostate pain syndrome

Laboratory diagnosis has been classically based on the four-glass test for bacterial localisation [267]. Besides sterile pre-massage urine (voided bladder urine-2), PPS shows < 10,000 cfu/mL of uropathogenic bacteria in expressed prostatic secretions and insignificant numbers of leukocytes or bacterial growth in ejaculates. However, this test is too complex for use by practising urologists. Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) [268, 269]. Overall, these tests help only a little in the diagnosis of PPS, because 8% of patients with suggested PPS have been found to have positive prostatic localisation cultures, similar to the percentage of asymptomatic men [270].

Bladder pain syndrome

Urine dipstick and urine culture (including culture for TB if sterile pyuria) are recommended in all patients suspected of having BPS. Urine cytology is also recommended in risk groups.

Gynaecological aspects of chronic pelvic pain

Vaginal and endocervical swabs to exclude infection are recommended.

4.2.6 **Invasive tests**

Anorectal pain

Anorectal manometry with sensory testing (pressure volume measurement: barostat) may be useful to diagnose dyssynergic defecation and hypersensitivity of the rectum which are typical for patients with CPP and IBS. Flexible rectosigmoidoscopy or colonoscopy should be considered in patients with anorectal pain to rule out coincidental colorectal pathology.

Laparoscopy for females

Laparoscopy is perhaps the most useful invasive investigation to exclude gynaecological pathology [271, 272] and to assist in the differential diagnosis of CPP in women [273]. Often, it is combined with cystoscopy [274, 275] and/or proctoscopy to help identify the site of multi-compartment pain.

Psychological considerations around laparoscopy

Three very different studies of laparoscopy suggest that it can improve pain through resolving concerns about serious disease [276], although showing women the photograph of their pelvic contents did not improve on explanation alone [277]; and integrating somatic and psychological assessment from the start rather than dealing with psychological concerns only after excluding organic causes of pelvic pain [278].

Cystoscopy and bladder biopsy

Despite controversy on the diagnostic and follow-up value of cystoscopy in BPS [279-283], this panel believes that objective findings are important for diagnosis, prognosis and ruling out other treatable conditions (a standardised scheme of diagnostic criteria will also contribute to uniformity and comparability of different studies [284]. Endoscopically, BPS type 3 displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit - the Hunner lesion [234]. The scar ruptures with increasing bladder distension, producing a characteristic waterfall type of bleeding. There is a strong association between BPS type 3 and reduced bladder capacity under anaesthesia [285]. Non-lesion disease displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign although they can be observed without BPS [286]. Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease [151, 178, 284, 287, 288]. Important differential diagnoses to exclude, by histological examination, are carcinoma *in situ* and tuberculous cystitis.

Table 4: ESSIC classification of BPS types according to results of cystoscopy with hydrodistension and biopsies [11]

	Cystoscopy with hydrodistension			
	Not done	Normal	Glomerulations ^a	Hunner's lesion ^b
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive ^c	XC	1C	2C	3C

^aCystoscopy: glomerulations grade 2-3

^bLesion per Fall's definition with/without glomerulations

^cHistology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

4.3 Diagnostic algorithm

Figure 1: Diagnosing chronic pelvic pain

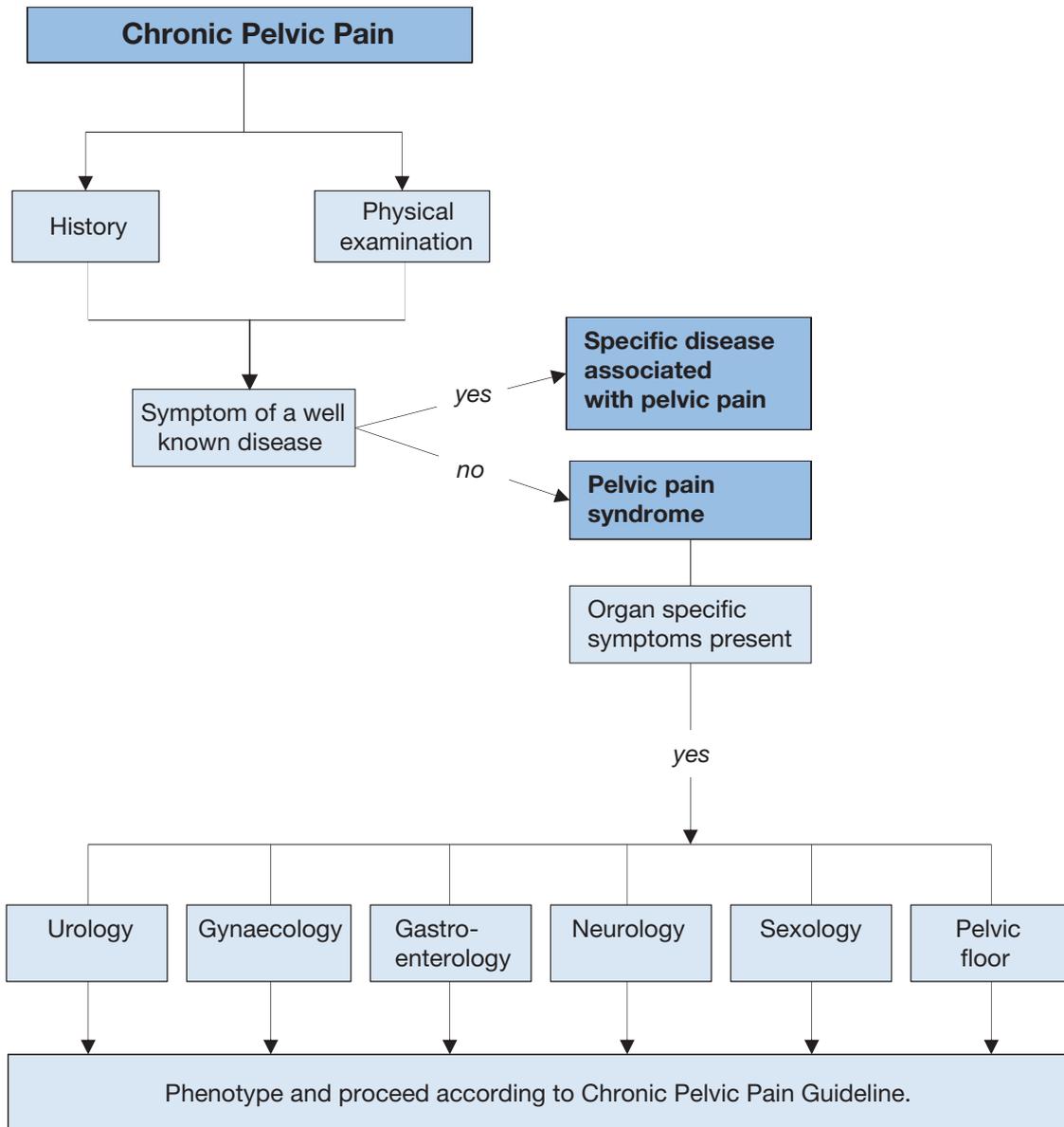


Figure 2: Phenotyping of pelvic pain - UPOINT classification

Phenotyping	Assessment
Urology	Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry,
Psychology	Anxiety about pain, depression and loss of function, history of negative sexual experiences
Organ specific	Ask for gynaecological, gastro-intestinal, ano-rectal, sexological complaints Gynaecological examination, rectal examination
Infection	Semen culture and urine culture, vaginal swab, stool culture
Neurological	Ask for neurological complaints (sensory loss, dysaesthesia). Neurological testing during physical examination: sensory problems, sacral reflexes and muscular function.
Tender muscle	Palpation of the pelvic floor muscles, the abdominal muscles and the gluteal muscles
Sexological	Erectile function, ejaculatory function, post-orgasmic pain

4.4 Other painful conditions without a urological cause

Dysmenorrhoea

Menstrual pain or 'dysmenorrhoea' may be primary or secondary. Primary dysmenorrhoea classically begins at the onset of ovulatory menstrual cycles and tends to decrease following childbirth [273]. Secondary dysmenorrhoea suggests the development of a pathological process, such as endometriosis [272], adenomyosis [289] or pelvic infection, which need to be excluded.

Infection

In pre-menopausal women, a history of pelvic inflammatory disease (PID) must be excluded. A patient's sexual history should be taken along with swabs to exclude chlamydia and gonorrhoea infection. Bacterial and viral genital tract pathogens should also be excluded [290], as they can cause severe pelvic/vaginal/vulvar pain [291] and are associated with ulcerating lesions and inflammation, which may lead to urinary retention [292]. If there is any doubt about the diagnosis, laparoscopy may be helpful, as one of the differential diagnoses is endometriosis.

Endometriosis and adenomyosis

The incidence of endometriosis is rising in the developed world. It has widespread impact on women's lives [293], with pain more important than physical findings in determining QoL [294]. The precise aetiology is unknown, but an association with infertility is recognised [295]. A diagnosis is usually made when a history of secondary dysmenorrhoea and/or dyspareunia exists. On examination, there is often tenderness in the lateral vaginal fornices, reduced uterine mobility, tenderness in the recto-vaginal septum, and on occasion, adnexal masses. Laparoscopy is the most useful diagnostic tool [296-298]. Endometriotic lesions affecting the urinary bladder or causing ureteric obstructions can occur, as well as lesions affecting the bowel, which may lead to rectal bleeding in association with menstruation. Adenomyosis is associated with augmented pain during menses. It is diagnosed by an US scan of the uterus, which often shows cystic dilatation of the myometrium [299].

Gynaecological malignancy

The spread of gynaecological malignancy of the cervix, uterine body or ovary will cause pelvic pain depending on the site of spread.

Injuries related to childbirth

Trauma occurring at the time of childbirth may lead to CPP related to the site of injury. Female sexual dysfunction is perhaps the commonest presenting problem [300]. There is often a transient problem with oestrogen deficiency in the post-partum period and during breastfeeding, which can compound this situation. Denervation of the pelvic floor with re-innervation may also lead to dysfunction and pain.

Pain associated with pelvic organ prolapse and prolapse surgery

Pelvic organ prolapse is often asymptomatic, unless it is so marked that it causes back strain, vaginal pain and skin excoriation [301]. Prolapse is often a disease of older women, and it is often associated with post-menopausal oestrogen deficiency, which may lead to pain associated with intercourse. Prolapse surgery may entail the use of non-absorbable mesh (usually in the form of “mesh kits”) [302-304]. Although they may have a role in supporting the vagina, they are also associated with several complications including bladder, bowel and vaginal trauma [303]. In a subset of these patients, chronic pain may ensue, because mesh insertion may cause nerve and muscle irritation [300]. Patients should be fully evaluated clinically and may need specialised imaging, using contrast mediums if necessary, to make a diagnosis.

Haemorrhoids

Chronic pelvic pain is rare in haemorrhoidal disease because endoscopic and surgical treatment is mostly effective in acute disease. The most frequent aetiology of pain without significant bleeding is thrombosed external haemorrhoids or an anal fissure. Haemorrhoidal pain on defecation associated with bleeding is usually due to prolapse or ulceration of internal haemorrhoids. Anaemia from haemorrhoidal bleeding is rare but may arise in patients on anti-coagulation therapy, or those with clotting disorders.

Anal fissure

Anal fissures are tears in the distal anal canal and induce pain during and after defecation. The pain can last for several minutes to hours. Persistence of symptoms beyond six weeks or visible transversal anal sphincter fibres define chronicity. Fissures located off the midline are often associated with specific diseases such as Crohn’s disease or anal cancer. Internal anal sphincter spasms and ischaemia are associated with chronic fissures.

Proctitis

Abdominal and pelvic pain in patients with inflammatory bowel disease and proctitis are often difficult to interpret. Faecal calprotectin may help to differentiate between inflammation and functional pain, to spare steroids.

Irritable bowel syndrome

Although IBS can be associated with pelvic pain, the authors of these guidelines consider a full discussion of this topic beyond the scope of these guidelines. A number of high quality clinical guidelines address this topic [305, 306].

4.5 Summary of evidence and recommendations: diagnostic evaluation**4.5.1 Diagnostic evaluation of PPS**

Summary of evidence	LE
Prostate pain syndrome is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.	2b
Prostate pain syndrome has no known single aetiology.	3
Pain in PPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
Prostate pain syndrome has a high impact on QoL.	2b
Depression and catastrophic thinking are associated with more pain and poorer adjustment.	3
The prevalence of PPS-like symptoms is high in population-based studies (> 2%).	2b
Reliable instruments assessing symptom severity as well as phenotypic differences exist.	2b

Recommendations	GR
Adapt diagnostic procedures to the patient. Specific diseases with similar symptoms must be excluded.	A
Use a validated symptom and quality of life scoring instrument, such as the National Institutes of Health Chronic Prostatitis Symptom Index, for initial assessment and follow-up.	B
Assess prostate pain syndrome associated negative cognitive, behavioural, sexual, or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.	B

4.5.2 **Diagnostic evaluation of BPS**

Summary of evidence	LE
BPS has no known single aetiology.	3
Pain in BPS does not correlate with bladder cystoscopic or histologic findings.	2a
BPS Type 3 C can only be confirmed by cystoscopy and histology.	2a
Lesion/non-lesion disease ratios of BPS are highly variable between studies.	2a
The prevalence of BPS-like symptoms is high in population-based studies.	2a
BPS occurs at a level higher than chance with other pain syndromes.	2a
BPS has an adverse impact on QoL.	2a
Reliable instruments assessing symptom severity as well as phenotypical differences exist.	2a

Recommendations	GR
Patients with bladder pain should undergo general anaesthetic rigid cystoscopy in accordance with European Society for the Study of Interstitial Cystitis guidelines.	A
After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with bladder pain syndrome (BPS) by subtype and phenotype.	A
Assess BPS associated non-bladder diseases systematically.	A
Assess BPS associated negative cognitive, behavioural, sexual, or emotional consequences.	A
Use a validated symptom and quality of life scoring instrument for initial assessment and follow-up.	B

4.5.3 **Diagnostic evaluation of scrotal pain syndrome**

Summary of evidence	LE
The nerves in the spermatic cord play an important role in scrotal pain.	2b
Ultrasound of the scrotal contents does not aid in diagnosis or treatment of scrotal pain.	2b
Post-vasectomy pain is seen in a substantial number of men undergoing vasectomy.	2b
Scrotal pain is more often noticed after laparoscopic than after open inguinal hernia repair.	1b

4.5.4 **Diagnostic evaluation of urethral pain syndrome**

Summary of evidence	LE
Urethral pain syndrome may be a part of BPS.	2a
Urethral pain involves mechanisms of neuroplasticity and neuropathic pain.	2b

4.5.5 **Diagnostic evaluation of gynaecological aspects chronic pelvic pain**

Summary of evidence	LE
Clinical history and examination are mandatory to making a diagnosis.	2a
Laparoscopy is well-tolerated and does not appear to have negative psychological effects.	1b

Recommendations	GR
All women with pelvic pain should have a full gynaecological history and evaluation, including laparoscopy to rule out a treatable cause (e.g. endometriosis).	A

4.5.6 **Diagnostic evaluation of anorectal pain syndrome**

Summary of evidence	LE
Tenderness on traction is the main criterion of the chronic anal pain syndrome.	1a

Recommendations	GR
Functional testing is recommended in patients with anorectal pain.	A

4.5.7 *Diagnostic evaluation of pudendal neuralgia*

Summary of evidence	LE
Multiple sensory and functional disorders within the region of the pelvis/urogenital system may occur as a result of injury to one or more of many nerves. The anatomy is complex.	2
There is no single aetiology for the nerve damage and the symptoms and signs may be few or multiple.	1
Investigations are often normal.	2
The peripheral nerve pain syndromes are frequently associated with negative cognitive, behavioural, sexual, or emotional consequences.	1

Recommendations	GR
Rule out confusable diseases.	A
If a peripheral nerve pain syndrome is suspected, early referral should occur to an expert in the field, working within a multi-disciplinary team environment.	B
Imaging and neurophysiology help diagnosis but image and nerve locator guided local anaesthetic injection is preferable.	B

4.5.8 *Diagnostic evaluation of sexological aspects in CPP*

Summary of evidence	LE
Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.	2a
Patients who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of PPS.	2b
Sexual dysfunctions are prevalent in patients with PPS.	2b
In men with PPS the most prevalent sexual complaints are erectile dysfunction and ejaculatory dysfunction.	3
In females with CPPS all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and "vaginismus".	2a
Vulvar pain syndrome is associated with BPS.	3
Women with BPS suffer significantly more from fear of pain, dyspareunia and decreased desire.	2a
Pelvic floor muscle function is involved in the excitement and orgasm phases of sexual response.	3
Chronic pain can cause disturbances in each of the sexual response cycle phases.	2b

Recommendations	GR
Patients presenting with symptoms suggestive for chronic pelvic pain syndrome, should be screened for abuse, without suggesting a causal relation with the pain.	B
The bio-psychosocial model should be applied in the evaluation of the effect of chronic pelvic pain syndrome on the sexual function of the patient.	B
The bio-psychosocial model should be incorporated in research into the role of chronic pelvic pain in sexual dysfunction.	B

4.5.9 *Diagnostic evaluation of psychological aspects of CPP*

Summary of evidence	LE
There is no evidence that distress generates complaints of pelvic pain, or that multiple symptoms suggest unreality of pain.	2b
Current or recent sexual abuse are possible contributory factors in pelvic pain.	2a

Recommendations	GR
Psychological distress is common in pelvic pain in women, but should be interpreted in the context of pain.	A
Ask patients what they think is the cause of their pain to allow the opportunity to inform and re-assure as appropriate.	B

4.5.10 *Diagnostic evaluation of pelvic floor function*

Summary of evidence	LE
The ICS classification is suitable for clinical practice.	2a
Over-activity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a
Over-activity of the pelvic floor muscles is an input to the central nervous system causing central sensitisation.	2b
There is no accepted standard for diagnosing myofascial trigger points.	2a
There is a relation between the location of trigger point and the region where the pain is perceived.	3

Recommendations	GR
Use ICS classification on pelvic floor muscle function and dysfunction.	A
In patients with chronic pelvic pain syndrome it is recommended to actively look for the presence of myofascial trigger points.	B

5. MANAGEMENT

The philosophy for the management of chronic pelvic pain is based on a bio-psychosocial model. This is a holistic approach with the patients' active involvement. Single interventions rarely work in isolation and need to be considered within a broader personalised management strategy.

The management strategy may well have elements of self-management. Pharmacological and non-pharmacological interventions should be considered with a clear understanding of the potential outcomes and end points. These may well include: psychology, physiotherapy, drugs and more invasive interventions.

Treatment philosophy

Providing information that is personalised and responsive to the patient's problems, conveying belief and concern, is a powerful way to allay anxiety [307]. Additional written information or direction to reliable sources of information is useful; practitioners tend to rely on locally produced material or pharmaceutical products of variable quality while endorsing the need for independent materials for patients [308].

5.1 Conservative management

5.1.1 *Pain education*

It is always valuable to include education about the causes of pain, including eliciting from patients their anxieties about undiscovered pathology and addressing them. Information improves adherence to treatment and underpins self-management, as shown in many other painful and non-painful disorders but not specifically in pelvic and abdominal pain.

5.1.2 *Physical therapy*

The physiotherapist is part of the pain management team, together with the pain doctor and the psychologist. The therapeutic options for physiotherapists may not be the same in every country. Physiotherapists can either specifically treat the pathology of the pelvic floor muscles, or more generally treat myofascial pain if it is part of the pelvic pain syndrome. In most studies that have been done looking at the effect of physiotherapy in pelvic pain, the treatment of the pelvic floor is only part of the pain management. In a review about physiotherapy in women with pelvic pain, it was concluded that recommendations for physiotherapy should be given with caution [309]. They found six RCTs of which three showed level 1b evidence with low-risk of bias. One of these three found that Mensendieck somatocognitive therapy showed a pain reduction after one year follow-up of 64%. This approach consists of myofascial relaxation and tension, improving posture and movement in combination with cognitive behaviour therapy (CBT) [310].

Pelvic floor muscle pain

Treating pelvic floor over-activity and myofascial trigger points should be considered in the management of CPP. Treatment should be done by specialised physiotherapists who are trained not only in the musculoskeletal aspects of pain, but also in the psychological mechanisms and the role of the CNS in chronic pain.

For patients with CPP and dysfunction of the pelvic floor muscles, it is very helpful to learn how to relax the muscles when the pain starts. By doing this, the circle of pain-spasm-pain can be interrupted. In the case of shortened muscles, relaxation alone is not enough. Stretching of the muscle is mandatory to regain length and function. Studies on physical therapy for pelvic floor pain syndrome have been sparse. A single blinded RCT with myofascial physical therapy and general massage was carried out in patients with prostate or bladder pain. The global response rate to treatment with massage was significantly better in the prostate than in the bladder pain group (57% vs. 21%). In the prostate pain group, there was no difference between the two treatment arms. In the bladder pain group, myofascial treatment did significantly better than the massage. Massage only improved complaints in the prostate pain group. The fact that the prostate pain group consisted of only men is mentioned as a possible confounding factor [311].

Myofascial trigger point release

Treatment of myofascial trigger points can be done by manual therapy, dry needling and wet needling. The evidence for all the different treatments is weak, with most studies showing no significant difference between these techniques, though most studies were small and heterogeneous with regards to the patients and methods. There is no evidence that manual techniques are more effective than no treatment [312]. Most studies of dry needling have compared with wet needling. Different systematic reviews have come to the conclusion that, although there is an effect of needling on pain, it is neither supported nor refuted that this effect is better than placebo [313]. Other reviews have concluded that the same is true for the difference between dry and wet needling [314, 315].

Physiotherapy in BPS

General muscular exercise may be beneficial in some BPS patients [316]. Transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in BPS patients with high-tone dysfunction of the pelvic floor significantly improved several assessment scales [317]. The role of specific levator ani trigger point injections in women with CPP has been studied [318]. Each trigger point was identified by intravaginal palpation and injected with bupivacaine, lidocaine and triamcinolone. Seventy-two percent of women improved with the first trigger point injection, with 33% being completely pain-free. Efficacy and safety of pelvic floor myofascial physical therapy has been compared with global therapeutic massage in women with BPS; global response assessment (GRA) rate was 59% and 26%, respectively. Pain, urgency and frequency ratings, and O'Leary-Sant IC Symptom and Problem Index decreased in both groups during follow-up, and did not differ significantly between the groups. This suggests that myofascial physical therapy is beneficial in women with BPS [319].

Anal Pain Syndrome

In a recently published RCT, it is demonstrated that biofeedback treatment was superior to electrogalvanic stimulation and massage for treating chronic anal pain syndrome [139]. One hundred and fifty-seven patients who had at least weekly rectal pain were investigated, but only patients with tenderness on traction of the pelvic floor showed a significant treatment benefit. In patients with tenderness of the puborectalis muscle (Rome II: Highly likely Levator Ani Syndrome), 87% reported adequate relief after one month of biofeedback vs. 45% for electrogalvanic stimulation, and 22% for massage. These results were maintained at twelve months with adequate relief after nine sessions of biofeedback in 58% of the whole group (Rome II: Highly likely and Possible Levator Ani Syndrome), after galvanic stimulation in 27% and massage in 21% of patients. As previously described in dyssynergic defecation, the ability to expel a 50 mL water filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome [139]. The pathophysiology of the chronic anal pain syndrome is therefore similar to that of dyssynergic defecation, and this favours the role of the pelvic floor muscles in the pathophysiology of both conditions. Other treatment modalities have been less successful.

Treatment of sexual dysfunctions and CPP

Couples often benefit from early referral for relationship and sexual counselling during their treatment course [320]. Specific behavioural strategies for women who have urogenital complaints and female sexual dysfunction often include exploring alternatives to sexual intercourse (manual or oral pleasuring), different coital positions (female superior or side lying), and pacing, such as limiting thrusting to less than that causes pain. Planning for the time of intercourse is important, and scheduling a clinic visit after intercourse might be useful to identify specific sites and causes of post-coital flares. The corresponding evidence in men is lacking.

Other behavioural changes involve pre- and post-coital voiding, application of ice packs to the genital or suprapubic area [320, 321], and use of vaginal dilators before penile penetration. An alternative is to use natural dilators such as different fingers or sex toys. Hypoallergenic non-irritating lubricants can be used to reduce vulvar, urethral, and vaginal friction, and women with signs of vulvovaginal atrophy may benefit from introital

application of minimally absorbed locally applied oestrogen cream [322]. In patients with an overactive pelvic floor, referral for physical therapy, myofascial release, and internal pelvic floor muscle massage may offer relief [323].

Other physical therapy interventions

Electromagnetic therapy. A small, sham-controlled, double-blind study of four weeks showed a significant, sustained effect over a one-year period for CPPS [324].

Microwave thermotherapy. In uncontrolled studies significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy [325, 326].

Extracorporeal shockwave therapy. A small sham-controlled double-blind study of four times weekly perineal extracorporeal shockwave therapy (n=30) in men with chronic pelvic pain syndrome showed significant improvement in pain, QoL, and voiding compared to the control group (n=30) over twelve weeks [327]. Two other randomised sham-controlled studies, have been published more recently, one comparing ten treatment sessions over two weeks (n=40 vs. n=40) [328], another with four times weekly treatments (n=20 vs. n=20) [329]. Both concluded there was a significant effect in terms of total NIH-CPSI score and pain at twelve weeks. Unfortunately, no long term effects at 24 weeks could be shown in a published follow-up study of the second [330].

Acupuncture. In a small three-arm randomised trial of CPPS in men, electro-acupuncture was superior to sham treatment and advice and exercise alone [331]. Another more recent randomised study comparing acupuncture (n=50) versus sham-controlled (n=50) once weekly treatment for six weeks showed significant long lasting improvement at 24 weeks in terms of response rate and overall symptom scores [332]. Two systematic reviews and meta-analyses have been published in 2016 analysing seven randomised-controlled studies on a total of 471 participants comparing acupuncture to sham control or oral medical treatment [333, 334]. Both came to the conclusion that acupuncture was effective and safe, significantly reducing total NIH-CPSI scores compared to sham or medical treatment, and should be considered as a treatment option. However, the durability of this effect is not known.

Posterior tibial nerve stimulation. One sham-controlled medium-sized study (n=89) demonstrated significant improvement in total NIH-CPSI score and visual analogue scale for pain in men with category IIIB chronic prostatitis/CPP [335].

Transcutaneous electrical nerve stimulation. Despite the popularity of transcutaneous electrical nerve stimulation (TENS) and the number of trials undertaken, a systematic review has been unable to provide good evidence for or against its use in the management of chronic pain [336]. Furthermore, rigorous trials should be undertaken to provide some clarity for a commonly used intervention.

5.1.3 Psychological therapy

Psychological interventions may be directed at pain itself or at adjustment to pain as shown by improved function and mood and reduced health-care use with or without pain reduction. Ideally, treatment follows general principles and practice in the field of chronic pain [337, 338], but these have been neglected in pelvic pain. Two systematic reviews and meta-analyses of the few heterogeneous trials of psychologically based treatment for pelvic pain [339, 340] found some short term benefits for pain, of around 50%, comparable to that from pharmacotherapy, but this was not sustained at follow-up. Surprisingly, the single component treatments for chronic pelvic pain, counselling about US results [262], and emotional disclosure [341], showed improvements in pain, while three more standard multi-component (including psychological) treatments for pain [278, 310, 342] did not. A more recent RCT of multi-component treatment also showed no effect on pain but benefits for distress [343], as did an RCT of mindfulness meditation for women with bladder pain [344]. The importance of multi-disciplinary treatment is emphasised by several reviews [38, 345, 346], and the need for high quality psychological treatment evaluation is underlined [345]. For less disabled and distressed patients, this can be delivered in part over the internet [347]. Several other reviews make positive comments on psychological involvement [348], and recommend addressing psychological concerns from the outset, directed at the pain itself, with the intended outcome of reducing its impact on life [30], or at adjustment to pain, with improved mood and function and reduced health-care use, with or without pain reduction [31]. A good model of such an intervention, albeit a pilot study, is by Tripp et al [349] for men with chronic pelvic pain.

5.1.4 Dietary treatment

Scientific data are limited and dietary restriction alone does not produce significant symptomatic relief, however, consider the involvement of a dietician.

5.2 Pharmacological management

5.2.1 *Drugs for chronic pelvic pain syndrome*

In this section the evidence available for specific CPPSs is presented. Where there is no evidence the reader is directed to the section on analgesics below (5.2.3) where more generic use is discussed. There is a large discrepancy in the treatment effects reported in case series and controlled trials that results from a large placebo effect or publication bias. As a result of the multifactorial origin of for example PPS, one reason for treatment failure in some large randomised placebo-controlled trials may be the heterogeneity of the patient population. One strategy for improving treatment effects may be stratification of patient phenotypes. A prospective series of phenotypically directed treatment for PPS has shown significant improvement of symptoms and QoL [263, 350]. Monotherapeutic strategies for the treatment of PPS may fail [263], therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past ten years, results from RCTs have led to advances in standard and novel treatment options.

5.2.1.1 *Mechanisms of action*

Mechanisms of action are discussed as appropriate under the drugs headings below.

5.2.1.2 *Comparisons of agents used in pelvic pain syndromes*

Prostate Pain Syndrome (PPS)

Anti-inflammatory drugs

For non-steroidal anti-inflammatory agents (NSAIDs), a trial with celecoxib reported that the pain subscore, QoL subscore, and total NIH-CPSI score were in favour of the treatment arm vs. placebo, but effects were limited to the duration of therapy [264]. In a meta-analysis, two studies of NSAIDs [264, 270] and one with prednisolone [260] were pooled. Anti-inflammatory drugs were 80% more likely to have a favourable response than placebo. An updated network meta-analysis with more restrictive inclusion criteria regarding documented outcome measures but a wider spectrum of drugs (including glycosaminoglycans, phytotherapy and tanezumab) a significant effect on total NIH-CPSI scores and treatment response rates could be demonstrated. Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies are needed for confirmation, and long-term side-effects have to be taken into account.

α -blockers

Positive results from RCTs of α -blockers, i.e. terazosin [351, 352], alfuzosin [353], doxazosin [354, 355], tamsulosin [356, 357], and silodosin [358] have led to widespread use of α -antagonists in the treatment of PPS in recent years. Whereas one systematic review and classic meta-analysis has not reported a relevant effect of α -blockers due to study heterogeneity [359], another network meta-analysis of α -blockers [360] has shown significant improvement in total symptoms, pain, voiding, and QoL scores. In addition, they had a higher rate of favourable response compared to placebo [relative risk (RR) 1.4, 95% confidence interval (CI) 1.1-1.8, $P=0.013$]. However, treatment responsiveness, i.e. clinically perceptible or significant improvement, may be lower than expected from the change in mean symptom scores. Overall, α -blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPS patients [361]. Future studies should show if longer duration of therapy or some sort of phenotypically directed (e.g. patients with PPS and relevant voiding dysfunction) treatment strategies will improve treatment outcomes.

Antibiotic therapy

Empirical antibiotic therapy is widely used because some patients have improved with antimicrobial therapy. Patients responding to antibiotics should be maintained on medication for four to six weeks or even longer. Unfortunately, culture, leukocyte and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPS [362], and prostate biopsy culture findings do not differ from those of healthy controls [363]. The only randomised placebo-controlled trials of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (six weeks) [144], levofloxacin (six weeks) [364], and tetracycline hydrochloride (twelve weeks) [365]. The studies have been analysed in published meta-analyses [360, 366]. Although direct meta-analysis has not shown significant differences in outcome measures, network meta-analysis has suggested significant effects in decreasing total symptom, pain, voiding, and QoL scores compared with placebo. Combination therapy of antibiotics with α -blockers has shown even better outcomes in network meta-analysis. Despite significant improvement in symptom scores, antibiotic therapy did not lead to statistically significant higher response rates [366]. In addition, the sample sizes of the studies were relatively small and treatment effects only modest and most of the time below clinical significance. It may be speculated that patients profiting from treatment have had some unrecognised uropathogens. If antibiotics are used, other therapeutic options should be offered after one unsuccessful course of a quinolone or tetracycline antibiotic over six weeks.

5- α -reductase inhibitors

Although a few small pilot studies with 5- α -reductase inhibitors supported the view that finasteride may improve voiding and pain, the first RCT published in a peer-reviewed journal did not support this, but the study did lack power [367]. In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a one-year period, but lacked a placebo-control arm [368]. A six-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because of a lack of statistical power [369]. The NIH-CPSI scores decreased significantly in a subgroup of men enrolled in a prostate cancer risk reduction study treated with dutasteride compared to placebo [370]. Patients (n=427, age 50 to 75, elevated prostate-specific antigen) were included if they had significant “prostatitis-like” symptoms at baseline. Based on the evidence, 5- α -reductase inhibitors cannot be recommended for use in PPS in general, but symptom scores may be reduced in a restricted group of older men with an elevated PSA [370].

Phytotherapy

Phytotherapy applies scientific research to the practice of herbal medicine. An adequately powered placebo-controlled RCT of a pollen extract (Cernilton), showed clinically significant symptom improvement over a twelve-week period in inflammatory PPS patients (NIH Cat. IIIA) [371]. The effect was mainly based on a significant effect on pain. Another pollen extract (DEPROX 500) has been shown to significantly improve total symptoms, pain and QoL compared to ibuprofen [372]. Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT [373]. In contrast, treatment with saw palmetto, most commonly used for benign prostatic hyperplasia, did not improve symptoms over a one-year period [368]. In a systematic review and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo [360]. In addition, overall response rate in network meta-analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1-1.6).

Pregabalin is an anti-epileptic drug that has been approved for use in neuropathic pain. In an adequately powered randomised placebo-controlled study, which was the only report included in a recently published Cochrane review [374], a six-week course of pregabalin (n=218) compared to placebo (n=106) did not result in a significant reduction of NIH-CPSI total score [375].

Pentosane polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. One study using oral high-dose (3x 300 mg/day) demonstrated a significant improvement in clinical global assessment and QoL over placebo in men with PPS, suggesting a possible common aetiology [376].

Muscle relaxants (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal muscle spasm, but there have been few prospective clinical trials to support these claims. In one RCT, a triple combination of a muscle relaxant (thiocolchicoside), an anti-inflammatory drug (ibuprofen) and an α -blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an α -blocker alone [355].

Botulinum toxin type A (BTX-A) showed some effect in the global response assessment and the NIH-CPSI pain subdomain score in a small randomised placebo-controlled study of perineal skeletal muscle injection (100 U). However, patient numbers were low (thirteen in the (BTX-A) group and sixteen in the placebo group), and follow-up was too short to draw definitive conclusions. Side-effects are unclear [377]. In another randomised-controlled study of intraprostatic injection of BTX-A (100 or 200 U depending on prostate volume) versus placebo (n=30 in both groups) a significant improvement of total NIH-CPSI and subdomain scores could be shown at six months [378]. However, no real placebo effect could be demonstrated, which suggests unblinding. No definitive conclusion can be drawn.

Zafirlukast, a leukotriene antagonist, and prednisone in two low-power placebo-controlled studies failed to show a benefit [260, 379]. More recently, a placebo-controlled phase IIa study of tanezumab, a humanised monoclonal antibody against the pain mediating neurotrophin, nerve growth factor, failed to demonstrate significant effect [380].

Tanezumab is a humanised monoclonal antibody that specifically inhibits nerve growth factor (NGF), and should only be used in clinical trials.

Allopurinol

There is insufficient evidence for the use of allopurinol in PPS [381, 382].

Bladder Pain Syndrome

Treatments of significant value for BPS

Anti-histamines

Mast cells may play a role in BPS. Histamine is one of the substances released by mast cells. Histamine receptor antagonists have been used to block the H1 [383] and H2 [384] receptor subtypes, with variable results. A prospective placebo-controlled RCT of hydroxyzine or oral pentosane polysulphate did not show a significant effect [385].

Amitriptyline

Amitriptyline is a tricyclic antidepressant. Several reports have indicated improvement of BPS symptoms after oral amitriptyline [107, 386, 387]. Amitriptyline has been shown to be beneficial when compared with placebo plus behavioural modification [388]. Drowsiness is a limiting factor with amitriptyline, nortriptyline is sometimes considered instead.

Pentosane polysulphate

Is a semi-synthetic drug manufactured from beech-wood hemicellulose. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported [389, 390]. Pentosane polysulphate had a more favourable effect in BPS type 3C than in non-lesion disease [391]. Response was not dose dependent but related more to treatment duration. At 32 weeks, about half the patients responded. Combination therapy showed a response rate of 40% compared to 13% with placebo. For patients with an initial minor response to pentosane polysulphate, additional subcutaneous heparin was helpful [392, 393].

Immunosuppressants

Azathioprine treatment has resulted in disappearance of pain and urinary frequency [394]. Initial evaluation of cyclosporin A (CyA) [395] and methotrexate [396] showed good analgesic effect but limited efficacy for urgency and frequency. Corticosteroids are not recommended in the management of patients with BPS because of a lack of evidence.

Intravesical Treatments

Intravesical drugs are administered due to poor oral bio-availability establishing high drug concentrations within the bladder, with few systemic side-effects. Disadvantages include the need for intermittent catheterisation which can be painful in BPS patients, cost and risk of infection [397].

- **Local anaesthetics**

There are sporadic reports of successful treatment of BPS with intravesical lidocaine [398, 399]. Alkalisiation of lidocaine improves its pharmacokinetics [400]. Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after two weeks in 80% [401]. Intravesical instillation of alkalisied lidocaine or placebo for five consecutive days resulted in significantly sustained symptom relief for up to one month [402].

- **Hyaluronic acid and chondroitin sulphate** are described to repair defects in the glycosaminoglycan (GAG) layer. Despite the fact that intravesical GAG replenishment has been in use for about twenty years for BPS/IC, most of the studies are uncontrolled and with a small number of patients. Based on the studies available there are differences by virtue of substance classes, whether they are natural GAG layer components, dosage formulations, or concentrations. More important, there are differences in proven efficacy. RCTs are only published for chondroitin sulphate, a combination containing chondroitin sulfate and hyaluronic acid and pentosane polysulphate. One large prospective non-randomised study indicated hyaluronic acid significantly ameliorated sexual functions domains in IC/BPS patients [403]. It is well documented that intravesical instillations are a valuable and beneficial therapy, but distinct patient groups need to be confirmed by definite diagnostic findings [404].

- **Intravesical heparin**

Bladder pain syndrome patients were treated with heparin for three months, and over half had control of symptoms, with continued improvement after one year of therapy [405]. Kuo reported another trial of intravesical heparin for three months in women with frequency-urgency syndrome and a positive potassium test. Symptomatic improvement was reported in 80% of BPS patients [406]. Intravesical heparin plus dorsal tibial nerve stimulation in patients with refractory BPS was studied and it was shown that voiding frequency, pain score and maximum cystometric capacity were significantly better after two and twelve months [407].

Hyperbaric oxygen (HBO) has a moderate effect on a small subgroup of BPS patients. Disadvantages include high cost, limited availability of treatment sites, and time-consuming treatment [126].

Treatments of limited value for BPS

Cimetidine

There is limited data to suggest that cimetidine improves symptoms of BPS in the short-term [408]. Compared with placebo for three months, cimetidine significantly improved symptom scores, pain and nocturia, although the bladder mucosa showed no histological changes in either group [409].

Prostaglandins

Misoprostol is a prostaglandin that regulates various immunological cascades. After three months of treatment with misoprostol, 14/25 patients had significantly improved, with twelve showing a sustained response after a further six months [410]. The incidence of adverse drug effects was 64%.

L-Arginine

Oral treatment with the nitric oxide (NO) synthase substrate L-arginine decreases BPS-related symptoms [134, 411, 412]. Nitric oxide is elevated in patients with BPS [413]. However, others have not demonstrated symptomatic relief or changes in NO production after treatment [414, 415].

Oxybutynin is an anti-cholinergic drug used in overactive detrusor dysfunction. Intravesical oxybutynin combined with bladder training improves functional bladder capacity, volume at first sensation, and cystometric bladder capacity [416]. However, an effect on pain has not been reported.

Duloxetine (a serotonin-noradrenaline reuptake inhibitor antidepressant with a licence for the management of neuropathic pain) did not significantly improve symptoms of BPS [417]. Administration was safe, but tolerability was poor due to nausea. Based on these preliminary data, duloxetine cannot be recommended for treatment of BPS.

Clorpactin is a derivative of hypochloric acid previously used to treat BPS [418-422]. Due to high complication rates, clorpactin instillations can no longer be recommended [418, 419, 421, 423, 424].

Dimethyl sulphoxide (DMSO) and **Bacillus Calmette Guérin** (BCG) have been used in the past. There is insufficient evidence to recommend the use of either.

Scrotal Pain Syndrome

Treatment of chronic scrotal pain is based on the principles of treating chronic pain syndromes, as described throughout these guidelines [425].

Chronic gynaecological pain

It is difficult to compare the wide variation of drugs from an efficacy and safety perspective as they have such diverse uses/indications.

In those gynaecological patients where CPP is unrelated to any of the well-defined conditions, it is often difficult to determine a therapeutic pathway other than a multi-disciplinary chronic abdomino-pelvic pain management plan. A Cochrane review suggests there may be some evidence (moderate) supporting the use of progestogens. Though efficacious, physicians need to be conversant with progestogenic side effects (e.g. weight gain, bloatedness - the most common adverse effects) which can stop some patients from accepting such medication. Gonadotrophins, such as goserelin, are also thought to help such pain. However, when compared with progestogens, their efficacy remains limited, as is the case when comparing gabapentin with amitriptyline. The quality of evidence is generally low and is drawn from single studies [339].

Current hormonal contraceptives (e.g. the combined oral contraceptive pill and the progesterone-only pill), and intrauterine contraceptive devices (Mirena IUS™) have multiple biologic effects. Their mechanism of action maybe via a primary or secondary contraceptive action. For combined oral contraceptives and progestin-only methods, the main mechanisms are ovulation inhibition and changes in the cervical mucus that inhibit sperm penetration. The hormonal methods, particularly the low-dose progestin-only products and emergency contraceptive pills, have effects on the endometrium that, theoretically, could affect implantation. Their effectiveness as contraceptives range from 92-99.9% [261]. The precise mechanism of intrauterine contraceptive devices is unclear. Current evidence indicates they exert their primary effect before fertilisation, reducing the opportunity of sperm to fertilise an ovum. Their efficacy approaches 99% [426].

Gonadotropin-releasing hormone (GnRH) bind to specific receptors on pituitary gonadotrophs. Prolonged activation of GnRH receptors by GnRH leads to desensitisation and consequently to suppressed gonadotropin secretion. By contrast, GnRH antagonists compete with GnRH for receptors on gonadotropin cell membranes, inhibit GnRH-induced signal transduction and consequently gonadotrophin secretion. These compounds are free of agonistic actions, which might be beneficial in certain clinical applications, such as reducing the size of fibroids, endometrial bleeding and endometriosis [427].

Pelvic Floor and Chronic Anal Pain

Botulinum toxin type A (BTX-A) (pelvic floor)

Botulinum toxin A has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective [428]. Reviews do not support the injection of BTX-A into trigger points [429]. Pelvic floor muscle over-activity plays a role in CPP. BTX-A, as a muscle relaxant, can be used to reduce the resting pressure in the pelvic floor muscles. In women with high resting pressure in the pelvic floor muscles, it has been found that BTX-A lowers this pressure significantly. The magnitude of reduction was significantly higher than that in the placebo group. On the pain score (VAS), no intergroup differences were found in this relatively small randomised study [430]. BTX-A can also be injected at the sphincter level to improve urination or defecation. Relaxation of the urethral sphincter alleviates bladder problems and secondarily the spasm. In a cohort study of thirteen patients with CPP, BTX-A was injected into the external urethral sphincter. Subjectively, eleven patients reported a substantial change in pain symptoms, from 7.2 to 1.6 on a VAS [431].

Botulinum toxin type A (BTX-A) (chronic anal pain syndrome)

In CPP associated with spasm of the levator ani muscles, treatment of the puborectalis and pubococcygeus muscle by BTX-A appears to be promising in some women, as shown in a pilot study (n=12). The inclusion criteria were dependent only on vaginal manometry with over-activity of the pelvic floor muscles, defined as a vaginal resting pressure > 40 cm H₂O. Although dyspareunia and dysmenorrhoea improved, non-menstrual pelvic pain scores were not significantly altered [432]. In the following double-blinded, randomised, placebo-controlled trial, the same group defined pelvic floor myalgia according to the two criteria of tenderness on contraction and hypertension (> 40 cm H₂O) and included 60 women. In this larger study, non-menstrual pelvic pain was significantly improved compared to those treated with placebo (VAS score 51 vs. 22; P=0.009). It was concluded therefore that BTX-A is effective at reducing pelvic floor-muscle associated pain with acceptable adverse effects such as occasional urinary and faecal stress incontinence [430]. However, recently, a small RCT failed to show any benefit of BTX-A [433].

Intermittent chronic anal pain syndrome

Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled β -2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration [434]. Other treatment options are topic diltiazem and BTX-A [435]. However, there is still some controversy regarding the duration of pain of intermittent chronic and chronic anal pain syndrome. RCTs often use different definitions, extending the pain duration (with a shift to chronic pain) in order to include more patients and to better evaluate the study-drug action.

Abdominal pain associated with Irritable Bowel Syndrome

Linacotide, a minimally absorbed peptide guanylate cyclase-C agonist at a dose of 290 μ g once daily significantly improved abdominal pain (48.9% vs 34.5% placebo-treated) and bowel symptoms associated with irritable bowel syndrome with constipation (IBS-C) over 26 weeks of treatment [436]. Diarrhoea was the most common adverse event in patients treated with linacotide (4.5%). However, although it is known to overlap with IBS pelvic pain, effect on the latter was not assessed in this study.

5.2.2 Analgesics

If the use of simple analgesics fails to provide adequate benefit, then consider using the neuropathic agents, and if there is no improvement, consider involving a specialist pain management centre with an interest in pelvic pain. CPP is well defined and involves multiple mechanisms as described in previous sections of chapters. The management requires a holistic approach with biological, psychological and social components. Few studies have specifically looked at medications used in CPP [437], therefore, a wider look at the literature has been undertaken and further specific research is required. The agents concerned are divided for ease of description. Combinations often provide a greater benefit than individual agents. They may also allow lower individual dosages and thus minimise side-effects. The aim of using these drugs is to allow patients to improve their QoL. This is best measured by assessing their function as well as pain severity. If the use of these agents does not allow this, then they should be withdrawn. Unfortunately, the failure of one agent does not exclude potential benefit of an alternative. If the benefit is limited by side-effects, then the lowest effective dose should

be found (by dose titration). Sometimes, patients will prefer a higher level of pain and have fewer side-effects.

5.2.2.1 *Mechanisms of action*

Mechanisms of action are discussed as appropriate under the drug headings below.

5.2.2.2 *Comparisons within and between groups in terms of efficacy and safety*

Paracetamol (acetaminophen)

Paracetamol is a well-tolerated analgesic in a class of its own. This is an antipyretic analgesic with a central mechanism of action [438]. It is often available over the counter without prescription. A recent review questions its routine use as a first line analgesic based on inadequate evidence of efficacy in many pain conditions including dysmenorrhoea [439]. It will not be effective for all patients and individual responses should be reviewed when deciding on longer term use.

Non-steroidal anti-inflammatory agents (NSAIDs)

These agents are anti-inflammatory, antipyretic analgesics that act by inhibiting the enzyme cyclooxygenase (COX). They have a peripheral effect, hence their use in conditions involving peripheral or inflammatory mechanisms. They are commonly used for pelvic pain, many are available over the counter and are usually well tolerated. There is no good evidence to suggest one NSAID over another for pelvic pain. Guidelines for use of NSAIDs and COX-2 selective agents have been developed. They have more side-effects than paracetamol, including indigestion, headaches and drowsiness.

The evidence for their benefit in CPP is weak or non-existent and are often limited by side-effects. For pelvic pain in which inflammatory processes are considered important, such as dysmenorrhoea [440], NSAIDs are more effective than placebo and paracetamol, but with a higher incidence of side-effects. For pelvic pain in which central mechanisms may be incriminated, such as endometriosis [441], then the evidence is lacking for NSAIDs despite their common use.

At a practical level, if NSAIDs are considered for use, they should be tried (having regard for the cautions and contraindications) and the patient reviewed for improvement in function as well as analgesia. If this is not achieved, or side-effects are limiting, then they should be withdrawn.

Neuromodulators

These are agents that are not simple analgesics but used to modulate neuropathic or centrally mediated pain. There are several classes commonly used with recognised benefits in pain medicine. They are taken on a regular basis, all have side-effects that may limit use in some patients. In the UK, the National Institute for Health and Clinical Excellence (NICE) has reviewed the pharmacological management of neuropathic pain [442]. Not all the agents are licensed for use in pain management but there is a history and evidence to demonstrate their benefit. The evidence for treatment of CPP is lacking but is present for other painful conditions. For this chapter, most of the evidence is from non-pelvic pain sources. The general method for using these agents is by titrating the dose against benefit and side-effects. The aim is for patients to have an improvement in their QoL, which is often best assessed by alterations in their function. It is common to use these agents in combination but studies comparing different agents against each other, or in combination, are lacking. Some of these agents are also used for specific conditions.

Antidepressants

Tricyclic antidepressants

The tricyclic antidepressants (TCAs) have multiple mechanisms of action including, blockade of acetylcholine receptors, inhibition of serotonin and noradrenaline re-uptake, and blockade of histamine H1 receptors. They also have anxiolytic effects [443] and are frequently limited by their side-effects. Tricyclic antidepressants have a long history of use in pain medicine and have been subjected to a Cochrane review [444], suggesting that they are effective for neuropathic pain. Amitriptyline is the most commonly used member at doses from 10 to 75 mg/day (sometimes rising to 150 mg/day). This is titrated against benefit or side-effects and can be taken at night [442]. Nortriptyline and imipramine are used as alternatives.

Other Antidepressants

Duloxetine is a serotonin-noradrenaline re-uptake inhibitor (SNRI) antidepressant licensed for use in depression, urinary stress incontinence and neuropathic pain. There is moderately strong evidence of benefit in diabetic neuropathy and fibromyalgia at a dose of 60 mg/day [445]. Side-effects are common and may result in its discontinuation.

Selective serotonin re-uptake inhibitors are antidepressants with fewer side-effects. They are effective for depression, but there have been insufficient studies to demonstrate their benefit in pelvic or neuropathic pain [444-446].

Anticonvulsants

Anticonvulsants are commonly used in the management of neuropathic pain. There are general studies and some looking more particularly at pelvic pain. Individual agents have been systematically reviewed. Their use is suggested in the NICE Neuropathic Guidelines [442].

Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit [447]. Trials have tended to be of short duration, showing only moderate benefit. There are side-effects; some of which may be serious. It is no longer a first choice agent. Other anticonvulsant agents are available with fewer serious side-effects.

Gabapentin is commonly used for neuropathic pain and has been systematically reviewed [448]. It provides good quality relief with NNT of approximately six. Side-effects are common, notably drowsiness, dizziness and peripheral oedema. For higher dose levels, reference should be made to local formularies, and many clinicians do not routinely exceed 2.4 g/day in divided doses (most commonly three times daily). One study of women with CPP has suggested that gabapentin alone or in combination with amitriptyline provides better analgesia than amitriptyline alone [449]. A more recent pilot study suggests that gabapentin is beneficial and tolerable; a larger study is required to provide a definitive result [450].

Pregabalin is a commonly used neuromodulator with good evidence of efficacy in some neuropathic conditions but the NNT varies depending on the condition [451]. The dose for benefit is in the range of 300 to 600 mg/day. The same systematic review found that doses less than 150 mg/day are unlikely to provide benefit. A review for chronic pelvic pain syndrome (prostate) only found a single reviewable study that does not show overall symptom improvement but suggests individual symptoms may improve (e.g. pain, QoL) and side-effects were common demonstrating the need for further robust studies [374]. As with gabapentin, side-effects are common and may not be tolerated by patients. A formal assessment of efficacy against side-effects is required with the patient in order to determine longer-term treatment. Other anticonvulsants are available but not commonly used for managing pain. Other agents can be used in the management of neuropathic pain but they are best administered only by specialists in the management of pain and familiar with their use. They tend to be considered after the standard options have been exhausted. As with all good pain management, they are used as part of a comprehensive multidimensional management plan.

Opioids

Opioids are used for chronic non-malignant pain and may be beneficial for a small number of patients. Often patients will stop taking oral opioids due to side-effects or insufficient analgesic effect [452]. They should only be used in conjunction with a management plan with consultation between clinicians experienced in their use. It is suggested that a pain management unit should be involved along with the patient and their primary care physician.

There are well established guidelines for the use of opioids in pain management as well as considering the potential risks [453]. There is also information available online for patients [454, 455]. Opioids Aware is a web-based resource for patients and healthcare professionals, jointly produced by the Faculty of Pain Medicine of Royal College of Anaesthetists and Public Health England, to support prescribing of opioid medicines for pain. <http://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/>. There are several agents available in the group. They can be divided into weak (e.g., codeine, dihydrocodeine and tramadol) or strong opioids (e.g., morphine, oxycodone, fentanyl and hydromorphone). Oral administration is preferable, but if poorly tolerated, a percutaneous (patch) route may have advantages. More invasive approaches are less commonly used and within the realms of specialist units. Side-effects are common, including constipation, nausea, reduced QoL, opioid tolerance, hormonal and immunological effects along with psychological changes and require active management.

There is a growing understanding of opioid-induced hyperalgesia; a situation in which patients taking opioids, paradoxically, become more sensitive to painful stimuli [456, 457]. This is another reason for these drugs to be used in a controlled fashion for long-term management of non-malignant pain.

Morphine is the standard opioid with which many physicians are familiar. The aim is to use a slow or sustained release preparation starting with a low-dose and titrating the dose every three days to one week against

improvement in both function and pain. Side-effects should also be monitored and managed accordingly. Particular attention should be paid to the management of constipation.

There are a variety of other agents available and some are mentioned below:

Transdermal fentanyl may be considered when oral preparations are restricted (e.g., ileostomy). It may also be beneficial when there are intolerable side-effects from other opioids.

Methadone has a long record of use as an opioid. There is a theoretical advantage of benefit with its N-methyl-D-aspartate receptor (NMDA) antagonist activity. This may be relevant in neuropathic pain [458].

Oxycodone may have greater efficacy than morphine in some situations, such as hyperalgesic states including visceral pain [459].

Tramadol is an established analgesic with dual effects on opioid receptors and serotonin release. More recently, tapentadol, has been released with opioid action and noradrenaline re-uptake inhibition. It is too early to assess its real value in the armamentarium for pain management.

5.3 Surgical management

5.3.1 Surgery

Bladder Pain Syndrome (BPS)

Bladder distension

Although bladder hydrodistension is a common treatment for BPS, the scientific justification is scarce. It can be part of the diagnostic evaluation, but has limited therapeutic role.

Hydrodistension and Botulinum toxin type A (BTX-A)

Botulinum toxin type A may have an antinociceptive effect on bladder afferent pathways, producing symptomatic and urodynamic improvements [115]. Treatment with hydrodistension and hydrodistension plus intravesical BTX-A has been compared [460]. There was symptomatic improvement in all patients. However, in the hydrodistension-only group, 70% returned to their previous symptoms after one month, while in the BTX-A-treated patients, VAS score and functional and cystometric bladder capacity improved at three months. Botulinum toxin type A trigonal-only injection seems effective and long-lasting as 87% of patients reported improvement after three months follow-up [461]. Over 50% reported continued benefit nine months after the first treatment. When re-treatment was needed, similar results were obtained. The authors concluded that this treatment is safe, effective and can be repeated. Adverse effects of BTX-A administration for IC/BPS were significantly less than for overactive bladder syndrome, namely in increased post-void residual volumes and decreased voiding efficiency [462]. Recent RCTs have confirmed benefits and long efficacy of BTX-A administration [463-466]. The AUA guidelines panel has recently upgraded BTX-A treatment from fifth to a fourth line treatment [467].

Transurethral resection (TUR), coagulation and laser

Endourological destruction of bladder tissue aims to eliminate urothelial, mostly Hunner lesions. Since the 1970s resection and fulguration have been reported to achieve symptom relief, often for more than three years [468, 469]. Prolonged amelioration of pain and urgency has been described for transurethral laser ablation as well [470].

Open Surgery for BPS

Bladder pain syndrome is benign and does not shorten life, thus operative procedures rank last in the therapeutic algorithm. There is no evidence that it relieves pain. Surgery for refractory BPS is only appropriate as a last resort for patients with refractory end-stage disease. Major surgery should be preceded by thorough pre-operative evaluation, with an emphasis on determining the relevant disease location and subtype. If surgery is considered, the panel's advice is to refer the patient to a specialist centre experienced in managing CPP with a multi-disciplinary team approach.

Four major techniques are common:

1. Urinary diversion without cystectomy. As early as 1967, it was reported that bladder augmentation without removal of the diseased tissue was not appropriate [471]. Reports that unresected BPS bladders cease to induce symptoms after loss of contact with urine are scarce [112, 472].

2. Supratrigonal cystectomy with subsequent bladder augmentation represents the most favoured continence-preserving surgical technique. Various intestinal segments have been used for supratrigonal augmentation [473-475].
3. Subtrigonal cystectomy. Subtrigonal resection has the potential of removing the trigone as a possible disease site, but at the cost of requiring ureteral reimplantation. Trigonal disease is reported in 50% of patients and surgical failure has been blamed on the trigone being left in place [476]. In contrast, another study [477] reported six out of seventeen patients being completely cured by supratrigonal resection [476]. A recent study on female sexuality after cystectomy and orthotopic ileal neobladder showed pain relief in all patients, but only one regained normal sexual activity [478].
4. Cystectomy with formation of an ileal conduit still ranks first in current USA practice trends for BPS surgery [479]. For cosmetic reasons, continent diversion is preferred, particularly in younger patients. After orthotopic bladder augmentation, particularly when removing the trigone, voiding may be incomplete and require intermittent self-catheterisation. Patients considering these procedures must be capable of performing, accepting and tolerating self-catheterisation. For patients with BPS who develop recurrent pain in the augmented bladder or continent pouch after enterocystoplasty or continent urinary diversion, retubularisation of a previously used bowel segment to form a urinary conduit has been recommended [480]. It is important to note that pregnancies with subsequent lower-segment Caesarean section have been reported after ileocystoplasty [480, 481].

Prostate Pain Syndrome (PPS)

There is no evidence for surgical management, including transurethral incision of the bladder neck, radical transurethral resection of the prostate or, in particular, radical prostatectomy in the management of chronic pain in patients with PPS. Recently, a large Chinese randomised-controlled trial of circumcision combined with a triple oral therapy (ciprofloxacin, ibuprofen, tamsulosin) versus oral therapy alone has been published for patients with PPS (total N=774) [482]. It is hypothesised that there may be some immunological interaction via pathogenic antigen presenting cells in the foreskin with CD4+ T cells causing autoimmunity to the prostate gland. They reported an improvement in total NIH-CPSI score and subdomain scores at twelve weeks. However, despite a large cohort, the study results are questionable because of the weak theoretical background, and a potential large placebo effect lacking a sham control. In addition, no long-term effectiveness has been reported. Before having an impact on recommendations, the results of this study have to be independently confirmed and the treatment effect must persist.

Testicular Pain Syndrome

Microsurgical denervation of the spermatic can be offered to patients with testicular pain. In a long term follow-up study, patients who had a positive result on blocking the spermatic cord were found to have a good result following denervation [483].

Chronic Anal Pain Syndrome

Chronic anal pain syndrome after stapled procedures, such as hemorrhoidopexy (PPH) or stapled trans-anal rectal resection (STARR) may respond to excision of the scarred staple line as shown in 21 consecutive patients with an overall improvement of pain in 85.7% of patients undergoing scar excision surgery [484]. An early scar excision before three to six months after pain onset was associated with better pain relief.

Urethral Pain Syndrome

There is no specific treatment that can be advised. Management should be multi-disciplinary and multi-modal [485]. Laser therapy of the trigonal region may be a specific treatment. One trial comparing two forms of laser reported good results, but did not compare with sham treatment [486]. The majority of publications on treatment of urethral pain syndrome have come from psychologists [180].

Presumed intra-abdominal adhesions

In gynaecological patients with CPP and presumed adhesions, there is no consensus as to whether adhesiolysis should be performed to improve pain [487, 488].

Extensive surgery for endometriosis is challenging and is still considered to be controversial, as there is at least one RCT showing no benefit in pain relief after the removal of early extensive endometriosis compared to sham surgery [489, 490].

In patients with adenomyosis, the only curative surgery is hysterectomy but patients can benefit from hormonal therapy and analgesics (see 5.2.1).

Pudendal Neuralgia and surgery

Decompression of an entrapped or injured nerve is a routine approach and probably should apply to the pudendal nerve as it applies to all other nerves. There are several approaches and the approach of choice probably depends upon the nature of the pathology. The most traditional approach is transgluteal; however, a transperineal approach may be an alternative, particularly if the nerve damage is thought to be related to previous pelvic surgery [187, 251, 491-495]. Currently, there has been only one prospective randomised study [493]. This study suggests that, if the patient has had the pain for less than six years, 66% of patients will see some improvement with surgery (compared to 40% if the pain has been present for more than six years). Surgery is not the answer for all patients. On talking to patients that have undergone surgery, providing the diagnosis was clear-cut, most patients are grateful to have undergone surgery but many still have symptoms that need management.

5.3.2 Neuromodulation

The role of neuromodulation in the management of pelvic pain should only be considered by specialists in pelvic pain management. These techniques are only used as part of a broader management plan and require regular follow-up. The research base is developing and the techniques broadening (e.g., spinal cord stimulation (SCS), sacral root stimulation, dorsal root ganglion stimulation or peripheral nerve stimulation). These are expensive interventional techniques for patients refractory to other therapies. Therefore, it is inappropriate to provide a detailed review in this publication. In the UK, guidance has been published for SCS in neuropathic pain [496]. This emphasises the comments above. This guidance suggests a trial period of stimulation before full implementation. Neuromodulation is still finding its role in pelvic pain management. There has been growing evidence in small case series or pilot studies, but more detailed research is required [497]. Its role in overactive bladder and faecal incontinence is more robust but is limited for pain.

Bladder Pain Syndrome

A comparison of sacral neuromodulation (SNM) vs. pudendal nerve stimulation (PNS), showed an overall 59% improvement in symptoms with PNS vs. 44% with SNM. Most patients who tested both a sacral and pudendal electrode chose PNS as the better site. Follow-up showed marked improvements in voiding variables and validated BPS symptom questionnaires. Over 90% of patients treated with neuromodulation stated that they would undergo implantation again [498]. Long-term results were verified in a retrospective study of patients from 1994 to 2008 [499]. Permanent SNM implantation was performed in patients who showed at least 50% improvement in symptoms with a temporary peripheral nerve evaluation test [499]. Median follow-up was 61.5 months. Good long-term success of SNM was seen in 72%, with a 28% explantation rate. The most frequent reason for explantation was poor outcome (54% of the failed patients). The revision rate was 50%. In a study of women who underwent permanent device implantation from 2002 to 2004 [448], mean pre-/post-operative pelvic pain and urgency/frequency scores were $21.61 \pm 8.6/9.22 \pm 6.6$, and mean pre-/post-operative visual analogue pain scale (VAPS) scores were $6.5 \pm 2.9/2.4 \pm 1.1$. Mean follow-up was 86 ± 9.8 months. Sacral neuromodulation showed adequate improvement for the symptoms of refractory BPS. The re-operation rate was 25%.

Pudendal Neuralgia

Pudendal neuralgia represents a peripheral nerve injury and as such should respond to neuromodulation by implanted pulse generators. However, it is important that the stimulation is perceived in the same site as the perceived pain. Spinal cord stimulation (SCS) may be effective for thoraco-lumbar afferents. However, it is difficult to obtain appropriate stimulation from SCS for the sacral nerves including pudendal. There is limited experience with sacral root stimulation and as a result stimulation for pudendal neuralgia should only be undertaken in specialised centres and in centres that can provide multi-disciplinary care [500-503].

Chronic Anal Pain Syndrome

In a large cohort of 170 patients with functional anorectal pain from the St. Mark's Hospital (Harrow, Middlesex, United Kingdom) sacral nerve stimulation was used in three patients (two improved), while biofeedback was the most used modality with the greatest treatment effect in patients with defecatory dysfunction (29 patients, 17 improved) [435]. Sacral neuromodulation has been reported to be somewhat beneficial in two uncontrolled studies, showing improvement in about half the patients [504, 505]. Martellucci *et al* have evaluated sacral neuromodulation in 27 patients, including 18 patients with previous pelvic surgery. Sixteen patients (59%) responded to testing and had a definitive implantation with long-term follow-up of 37 months with sustained response, while no patients after stapler surgery responded to neuromodulation [505]. Sacral neuromodulation

may be a choice in patients with CPP who failed to respond to biofeedback and drug therapy. The less invasive PTNS was tested in twelve women with CPP lasting for at least six months and showed an improvement in pain, QoL and sexual life [506]. No “sham” SNM or PTNS control group were used in either cited studies, which limits their value as an important placebo effect cannot be ruled out.

5.3.3 *Nerve blocks*

Nerve blocks for pain management are usually carried out by specialists in pain medicine as part of a broader management plan [61]. They may have a diagnostic or therapeutic role. Textbooks have been written on the subject and practitioners using them should be trained in appropriate patient selection, indications, risks and benefits. Many such interventions also require understanding and expertise in using imaging techniques to perform the blocks accurately. Diagnostic blocks can be difficult to interpret due to the complex mechanisms underlying the painful condition or syndrome. Sustained but limited benefit may lead to more permanent procedures (e.g., radiofrequency procedures). There is a weak evidence base for these interventions for chronic non-malignant pain.

Pudendal Neuralgia

The role of injections may be divided into two. First, an injection of local anaesthetic and steroid at the site of nerve injury may produce a therapeutic action. The possible reasons for this are related to the fact that steroids may reduce any inflammation and swelling at the site of nerve irritation, but also because steroids may block sodium channels and reduce irritable firing from the nerve [507]. The second possible benefit is diagnostic. It has already been indicated that when the pudendal nerve is injured there are several sites where this may occur. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [249-259].

Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, CT guidance, or the use of US. US avoids any radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block. Currently, infiltration of the pudendal nerve within Alcock’s canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed. Pulsed radio frequency stimulation has also been suggested as a treatment [508].

5.4 **Summary of evidence and recommendations: management**

5.4.1 *Management of PPS*

Summary of evidence	LE
Phenotypically directed treatment may improve treatment success.	3
α -blockers have moderate treatment effect regarding total pain-, voiding-, and QoL scores in PPS.	1a
Antimicrobial therapy has a moderate effect on total pain-, voiding-, and QoL scores in PPS.	1a
NSAIDs have moderate overall treatment effects on PPS.	1a
Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPS.	1a
Pentosane polysulphate improves global assessment and QoL score in PPS.	1b
There are insufficient data on the effectiveness of muscle relaxants in PPS.	2b
Pregabalin is not effective for the treatment of PPS.	1b
BTX-A injection into the pelvic floor (or prostate) may have a modest effect in PPS.	2b
Acupuncture is superior to sham acupuncture in improving symptoms and QoL.	1a
Posterior tibial nerve stimulation is probably effective for the treatment of PPS.	1b
Extracorporeal shock wave therapy is probably effective over the short term.	1b
There are insufficient data supporting the use of other surgical treatments, such as transurethral incision of the bladder neck, transurethral resection of the prostate, or radical prostatectomy in patients with PPS.	3
Cognitive behavioural therapy designed for PPS may improve pain and QoL.	3

Recommendations	GR
Offer multimodal and phenotypically directed treatment options for Prostate Pain Syndrome (PPS).	A
Single use of antimicrobial therapy (quinolones or tetracyclines) over a minimum of six weeks is recommended in treatment-naïve patients with a duration of PPS less than one year.	A
α -blockers are recommended for patients with a duration of PPS less than one year.	A
High-dose oral pentosane polysulphate is recommended in PPS.	A
Acupuncture is recommended for use in PPS.	B
Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended for use in PPS, but long-term side-effects have to be considered.	B
For PPS with significant psychological distress, psychological treatment focused on PPS is recommended.	B

5.4.2 Management of BPS

Summary of evidence	LE
There is insufficient data for the long-term use of corticosteroids.	3
Limited data exist on effectiveness of cimetidine in BPS.	2b
Amitriptyline is effective for pain and related symptoms of BPS.	1b
Oral pentosane polysulphate is effective for pain and related symptoms of BPS.	1a
Oral pentosane polysulphate plus subcutaneous heparin is effective for pain and related symptoms of BPS, especially in initially low responders to pentosane polysulphate alone.	1b
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical pentosane polysulphate is effective, based on limited data, and may enhance oral treatment.	1b
There are limited data on the effectiveness of intravesical heparin.	3
Intravesical chondroitin sulphate may be effective.	2b
There is insufficient data for the use of bladder distension as a therapeutic intervention.	3
Hydrodistension plus BTX-A is superior to hydrodistension alone.	1b
Intravesical Bacillus Calmette Guérin (BCG) is not effective in BPS.	1b
Transurethral resection (coagulation and laser) may be effective in BPS type 3C.	3
Sacral neuromodulation may be effective in BPS.	3
Pudendal nerve stimulation (PNS) is superior to SNM for treatment of BPS.	1b
Avoidance of some food and drink may reduce symptoms.	3
Outcome of cystectomy for BPS is variable.	3

Recommendations	GR
Offer sub-type and phenotype-oriented therapy for the treatment of Bladder Pain Syndrome (BPS).	A
Multimodal behavioural, physical and psychological techniques should always be considered alongside oral or invasive treatments of BPS.	A
Administer amitriptyline for use in BPS.	A
Offer oral pentosane polysulphate for the treatment of BPS.	A
Treatment with oral pentosane polysulphate plus subcutaneous heparin is recommended especially in low responders to pentosane polysulphate alone.	A
Administer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	A
Administer intravesical pentosane polysulphate before more invasive treatment alone or combined with oral pentosane polysulphate.	A
Administer submucosal injection of Botulinum toxin type A (BTX-A) plus hydrodistension if intravesical instillation therapies have failed.	A
All ablative organ surgery should be the last resort and undertaken by experienced and BPS knowledgeable surgeons only.	A
Offer intravesical hyaluronic acid before more invasive measures.	B
Offer intravesical chondroitin sulphate before more invasive measures.	B
Offer transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3 C only.	B
Offer neuromodulation before more invasive interventions.	B
Offer dietary advice.	C
Offer intravesical heparin before more invasive measures alone or in combination treatment.	C
Offer intravesical bladder wall and trigonal injection of BTX-A if intravesical instillation therapies have failed.	C
Corticosteroids are not recommended for long-term treatment.	C
Bladder distension is not recommended as a treatment of BPS.	C

5.4.3 **Management of scrotal pain syndrome**

Summary of evidence	LE
Microsurgical denervation of the spermatic cord is an effective therapy for scrotal pain syndrome.	2b
Vasovasostomy is effective in post-vasectomy pain.	2b
Orchiectomy is the last resort in treating scrotal pain syndrome.	4

Recommendations	GR
Start with general treatment options for chronic pelvic pain.	A
Inform about the risk of post-vasectomy pain when counselling patients planned for vasectomy.	A
To reduce the risk of scrotal pain, open instead of laparoscopic inguinal hernia repair is recommended.	A
It is recommended that during inguinal hernia repair all the nerves in the spermatic cord are identified.	A
For patients who are treated surgically, microsurgical denervation of the spermatic cord is recommended.	A
We recommend that orchiectomy should not be done, unless all other therapies, including pain management assessment, have failed.	C

5.4.4 **Management of urethral pain syndrome**

Summary of evidence	LE
There is no specific treatment for urethral pain syndrome.	4
In patients with significant distress associated with bladder or urethral symptoms, psychological treatment may be worth using to reduce distress and thereby improve function and QoL.	4

Recommendations	GR
Start with general treatment options for chronic pelvic pain.	A
It is recommended that patients with urethral pain syndrome are treated in a multi-disciplinary and multi-modal programme.	B
When patients are distressed, it is recommended to refer them for pain-relevant psychological treatment to improve function and quality of life.	B

5.4.5 **Management of gynaecological aspects of chronic pelvic pain**

Summary of evidence	LE
Therapeutic options, including pharmacotherapy and surgery, can treat endometriosis effectively.	1b
Psychological treatment (CBT or supportive psychotherapy) can improve pain and sexual and emotional function in vaginal and vulvar pain syndrome.	1b
All other gynaecological conditions (including dysmenorrhea, obstetric injury, pelvic organ prolapse and gynaecological malignancy) can be treated effectively using pharmacotherapy.	3

Recommendations	GR
Provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.	B
Provide a multi-disciplinary approach to pain management in persistent disease states.	B

5.4.6 **Management of anorectal pain syndrome**

Summary of evidence on functional anorectal pain	LE
Biofeedback is the preferred treatment for the chronic anal pain syndrome.	1a
Electrogalvanic stimulation is less effective than biofeedback.	1b
Botulinum toxin type A is effective.	1b
Percutaneous tibial nerve stimulation is effective in anal pain.	1b
Sacral neuromodulation is effective in anal pain.	3
Inhaled salbutamol is effective in intermittent chronic anal pain syndrome.	3

Recommendations for functional anorectal pain	GR
Bio-feedback treatment is recommended in patients with pelvic pain and dyssynergic defecation.	A
Offer botulinum toxin type A and electrogalvanic stimulation in chronic anal pain syndrome.	B
Offer percutaneous tibial nerve stimulation in chronic anal pain syndrome.	B
Offer sacral neuromodulation in chronic anal pain syndrome.	C
Offer inhaled salbutamol in intermittent chronic anal pain syndrome.	C

5.4.7 **Management of pudendal neuralgia**

Summary of evidence	LE
There are multiple treatment options with varying levels of evidence.	3

Recommendations	GR
Neuropathic pain guidelines are well-established. Standard approaches to management of neuropathic pain should be utilised.	A

5.4.8 **Management of sexological aspects in CPP**

Summary of evidence	LE
Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complaints.	2b

Recommendations	GR
Offer behavioural strategies to the patient and his/her partner to cope with sexual dysfunctions.	B
Training of the pelvic floor muscles is recommended to improve quality of life and sexual function.	B

5.4.9 *Management of pelvic floor dysfunction*

Summary of evidence	LE
Myofascial treatment is effective.	1b
Biofeedback improves the outcome of myofascial therapy.	1a
Trigger point release is effective in treating muscle and referred pain.	1a

Recommendations	GR
Apply myofascial treatment as first line treatment.	A
In patients with an overactive pelvic floor, bio-feedback is recommended as therapy adjuvant to muscle exercises.	A
When myofascial trigger points are found, treatment by pressure or needling is recommended.	A

5.4.10 *Management of chronic/non-acute urogenital pain by opioids*

Recommendations	GR
All other reasonable treatments must have been tried and failed, before considering opioid treatment.	A
The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with another physician (including the patient and their family doctor).	A
Where there is a history or suspicion of drug abuse, a psychiatrist or psychologist with an interest in pain management and drug addiction should be involved.	A

6. EVALUATION OF TREATMENT RESULTS

6.1 Evaluation of treatment

For patients with chronic visceral pain, a visit to the clinician is important because they can ask questions, talk about how the process is going and have some time with the caregiver who understands the nature of their pain. First evaluation should take place after about six weeks to see if the treatment has been successful or not. When necessary adaptations are made and a next evaluation is planned.

6.1.1 *Treatment has not been effective*

6.1.1.1 *Alternative treatment*

In cases where the treatment initiated did not have enough effect, an alternative approach is advised. The first thing to do is a thorough evaluation of the patients' or care providers' adherence to the treatment that was initiated. Ask the patient if they have taken the medication according to the prescription, if there were any side-effects and if there were any changes in pain and function. Adjustment of medication or dose schemes might help. Another important thing to do is to read the reports of other caregivers like the physiotherapist and the psychologist. Has the therapy been followed until the end, what was the opinion of the therapist about the changes that were observed. In cases where the sessions had been ended by the patient, ask the patient why they made that decision. Check if the patient has understood the idea behind the therapy that was prematurely stopped.

6.1.1.2 *Referral to next envelope of care*

If patients and doctors come to the conclusion that none of the therapies given showed enough effect, then referral to a next envelope of care is advised. Unfortunately, the terminology used to describe the nature and specialisation level of centres providing specialised care for visceral pain patients is not standardised and country based. This does not facilitate easy referral schemes. It is advised that patients are referred to a centre that is working with a multi-disciplinary team and nationally recognised as specialised in pelvic pain. Such a centre will re-evaluate what has been done and when available, provide specialised care.

6.1.1.3 *Self-management and shared care*

Patients who find themselves confronted with CPP for which there is no specific treatment option available, will have to live with their pain. They will need to manage their pain, meaning that they will have to find a way to deal with the impact of their pain on daily activities in all domains of life. Self-help programmes maybe advised

and can be of help. The patient may also benefit from shared care, which means that a caregiver is available for supporting the self-management strategies. Together with this caregiver the patient can optimise and use the management strategies.

6.1.2 **Treatment has been effective**

In cases where treatment has been effective the caregiver may pay attention to fallback prevention. If the patient feels the same pain again, it helps to start at an early stage with the self-management strategies that he/she has learned during the former treatment. By doing so they will have the best chance of preventing the development of pelvic pain syndromes again.

7. REFERENCES

1. Fall, M., *et al.*, EAU Guidelines on Chronic Pelvic Pain., in EAU Guidelines on Chronic Pelvic Pain. Presented at the 18th EAU Annual Congress Madrid 2003. 2003, European Association of Urology: Arnhem.
<https://uroweb.org/guideline/chronic-pelvic-pain/>
2. Fall, M., *et al.* EAU guidelines on chronic pelvic pain. *Eur Urol*, 2004. 46: 681.
<https://www.ncbi.nlm.nih.gov/pubmed/15548433>
3. Fall, M., *et al.*, EAU Guidelines on Chronic Pelvic Pain., in EAU Guidelines on Chronic Pelvic Pain. Presented at the 18th EAU Annual Congress Barcelona 2010. 2010, European Association of Urology: Arnhem.
<https://uroweb.org/guideline/chronic-pelvic-pain/>
4. Fall, M., *et al.* EAU guidelines on chronic pelvic pain. *Eur Urol*, 2010. 57: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/19733958>
5. Engeler, D.S., *et al.* The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. *Eur Urol*, 2013. 64: 431.
<https://www.ncbi.nlm.nih.gov/pubmed/23684447>
6. McMahon, S.B., *et al.* Visceral pain. *Br J Anaesth*, 1995. 75: 132.
<https://www.ncbi.nlm.nih.gov/pubmed/7577247>
7. Shoskes, D.A., *et al.* Clinical phenotyping of patients with chronic prostatitis/chronic pelvic pain syndrome and correlation with symptom severity. *Urology*, 2009. 73: 538.
<https://www.ncbi.nlm.nih.gov/pubmed/19118880>
8. Magri, V., *et al.* Use of the UPOINT chronic prostatitis/chronic pelvic pain syndrome classification in European patient cohorts: sexual function domain improves correlations. *J Urol*, 2010. 184: 2339.
<https://www.ncbi.nlm.nih.gov/pubmed/20952019>
9. Merskey, H., *et al.*, Classification of Chronic Pain. 1994, Seattle.
<http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf>
10. Krieger, J.N., *et al.* NIH consensus definition and classification of prostatitis. *JAMA*, 1999. 282: 236.
<https://www.ncbi.nlm.nih.gov/pubmed/10422990>
11. van de Merwe, J.P., *et al.* Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol*, 2008. 53: 60.
<https://www.ncbi.nlm.nih.gov/pubmed/17900797>
12. Longstreth, G.F., *et al.* Functional bowel disorders. *Gastroenterology*, 2006. 130: 1480.
<https://www.ncbi.nlm.nih.gov/pubmed/16678561>
13. Phillips, B, *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
14. Schneider, M.P., *et al.* What are the benefits and harms of electrical neuromodulation vs best clinical practice or no treatment in chronic pelvic pain (CPP)?. PROSPERO: International prospective register of systematic reviews, 2017: CRD42017054893.
https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054893
15. Breivik, H., *et al.* Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*, 2006. 10: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/16095934>

16. Choung, R.S., *et al.* Irritable bowel syndrome and chronic pelvic pain: a population-based study. *J Clin Gastroenterol*, 2010. 44: 696.
<https://www.ncbi.nlm.nih.gov/pubmed/20375730>
17. Fenton, B.W. Measuring quality of life in chronic pelvic pain syndrome. *Exp Rev Obstet Gynecol*, 2010. 5: 115.
<http://www.tandfonline.com/doi/abs/10.1586/eog.09.70?needAccess=true>
18. Baranowski, A.P. Chronic pelvic pain. *Best Pract Res Clin Gastroenterol*, 2009. 23: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/19647692>
19. Krieger, J., *et al.* Non-uological syndromes and severity of urological pain symptoms: Baseline evaluation of the national institutes of health multidisciplinary approach to pelvic pain study. *J Urol*, 2013. 1): e181.
<https://www.ncbi.nlm.nih.gov/pubmed/71031385>
20. Chuang, Y.C., *et al.* Increased risks of healthcare-seeking behaviors of anxiety, depression and insomnia among patients with bladder pain syndrome/interstitial cystitis: a nationwide population-based study. *Int Urol Nephrol*, 2015. 47: 275.
<https://www.ncbi.nlm.nih.gov/pubmed/25577231>
21. Mulak, A., *et al.* Irritable bowel syndrome as an interdisciplinary clinical problem. *Adv Clin Exp Med*, 2008. 17: 667.
http://www.dbc.wroc.pl/Content/2600/1111_Mula.pdf
22. Riedl, A., *et al.* Somatic comorbidities of irritable bowel syndrome: A systematic analysis. *J Psychosom Res*, 2008. 64: 573.
<https://www.ncbi.nlm.nih.gov/pubmed/18501257>
23. Savidge, C.J., *et al.* Psychological aspects of chronic pelvic pain. *J Psychosom Res*, 1997. 42: 433.
<https://www.ncbi.nlm.nih.gov/pubmed/9194016>
24. Anda, R.F., *et al.* The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci*, 2006. 256: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/16311898>
25. Raphael, K.G. Childhood abuse and pain in adulthood: more than a modest relationship? *Clin J Pain*, 2005. 21: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/16093741>
26. Raphael, K.G., *et al.* Childhood victimization and pain in adulthood: a prospective investigation. *Pain*, 2001. 92: 283.
<https://www.ncbi.nlm.nih.gov/pubmed/11323150>
27. Vehof, J., *et al.* Shared genetic factors underlie chronic pain syndromes. *Pain*, 2014. 155: 1562.
<https://www.ncbi.nlm.nih.gov/pubmed/24879916>
28. Tunitsky, E., *et al.* Bladder pain syndrome/interstitial cystitis in twin sisters. *J Urol*, 2012. 187: 148.
<https://www.ncbi.nlm.nih.gov/pubmed/20227820>
29. Roth, R.S., *et al.* Patient beliefs about pain diagnosis in chronic pelvic pain: relation to pain experience, mood and disability. *J Reprod Med*, 2011. 56: 123.
<https://www.ncbi.nlm.nih.gov/pubmed/21542529>
30. Berman, S.M., *et al.* Reduced brainstem inhibition during anticipated pelvic visceral pain correlates with enhanced brain response to the visceral stimulus in women with irritable bowel syndrome. *J Neurosci*, 2008. 28: 349.
<https://www.ncbi.nlm.nih.gov/pubmed/18184777>
31. Bajaj, P., *et al.* Endometriosis is associated with central sensitization: a psychophysical controlled study. *J Pain*, 2003. 4: 372.
<https://www.ncbi.nlm.nih.gov/pubmed/14622679>
32. Berkley, K.J., *et al.* Don't dismiss dysmenorrhea! *Pain*, 2011. 152: 1940.
<https://www.ncbi.nlm.nih.gov/pubmed/21514053>
33. Zondervan, K.T., *et al.* The community prevalence of chronic pelvic pain in women and associated illness behaviour. *Br J Gen Pract*, 2001. 51: 541.
<https://www.ncbi.nlm.nih.gov/pubmed/11462313>
34. Savidge, C.J., *et al.* Women's Perspectives on their Experiences of Chronic Pelvic Pain and Medical Care. *J Health Psychol*, 1998. 3: 103.
<https://www.ncbi.nlm.nih.gov/pubmed/22021346>
35. Price, J., *et al.* Attitudes of women with chronic pelvic pain to the gynaecological consultation: a qualitative study. *BJOG*, 2006. 113: 446.
<https://www.ncbi.nlm.nih.gov/pubmed/16489938>

36. Fry, R.P., *et al.* Sociopsychological factors in chronic pelvic pain: a review. *J Psychosom Res*, 1997. 42: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/9055210>
37. Martin, C.E., *et al.* Catastrophizing: A predictor of persistent pain among women with endometriosis at 1 year. *Human Reproduction*, 2011. 26: 3078.
<https://www.ncbi.nlm.nih.gov/pubmed/21900393>
38. Riegel, B., *et al.* Assessing psychological factors, social aspects and psychiatric co-morbidity associated with Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) in men - A systematic review. *J Psychosom Res*, 2014. 77: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/25300538>
39. Watkins, K.E., *et al.* Depressive disorders and panic attacks in women with bladder pain syndrome/ interstitial cystitis: a population-based sample. *Gen Hosp Psychiatry*, 2011. 33: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/21596207>
40. Chung, S.D., *et al.* Association between chronic prostatitis/chronic pelvic pain syndrome and anxiety disorder: a population-based study. *PLoS ONE [Electronic Resource]*, 2013. 8.
<https://www.ncbi.nlm.nih.gov/pubmed/23691256>
41. Latthe, P., *et al.* Factors predisposing women to chronic pelvic pain: systematic review. *BMJ*, 2006. 332: 749.
<https://www.ncbi.nlm.nih.gov/pubmed/16484239>
42. Hilden, M., *et al.* A history of sexual abuse and health: a Nordic multicentre study. *BJOG*, 2004. 111: 1121.
<https://www.ncbi.nlm.nih.gov/pubmed/15383115>
43. Lampe, A., *et al.* Chronic pelvic pain and previous sexual abuse. *Obstet Gynecol*, 2000. 96: 929.
<https://www.ncbi.nlm.nih.gov/pubmed/11084180>
44. Angst, J. Sexual problems in healthy and depressed persons. *Int Clin Psychopharmacol*, 1998. 13 Suppl 6: S1.
<https://www.ncbi.nlm.nih.gov/pubmed/9728667>
45. Leonard, L.M., *et al.* Sexual functioning in women reporting a history of child sexual abuse: review of the empirical literature and clinical implications. *Annu Rev Sex Res*, 2002. 13: 346.
<https://www.ncbi.nlm.nih.gov/pubmed/12836736>
46. McGowan, L., *et al.* Chronic pelvic pain: A meta-analytic review. *Psychol Health*, 1998. 13: 937.
<http://www.tandfonline.com/doi/abs/10.1080/08870449808407441>
47. Roelofs, K., *et al.* Trauma and medically unexplained symptoms towards an integration of cognitive and neuro-biological accounts. *Clin Psychol Rev*, 2007. 27: 798.
<https://www.ncbi.nlm.nih.gov/pubmed/17728032>
48. Walker, E.A., *et al.* Psychiatric diagnoses and sexual victimization in women with chronic pelvic pain. *Psychosomatics*, 1995. 36: 531.
<https://www.ncbi.nlm.nih.gov/pubmed/7501783>
49. Nickel, J.C., *et al.* Childhood sexual trauma in women with interstitial cystitis/bladder pain syndrome: a case control study. *Can Urol Assoc J*, 2011. 5: 410.
<https://www.ncbi.nlm.nih.gov/pubmed/22154637>
50. Paras, M.L., *et al.* Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis. *JAMA*, 2009. 302: 550.
<https://www.ncbi.nlm.nih.gov/pubmed/19654389>
51. Campbell, R., *et al.* Gynecological health impact of sexual assault. *Res Nurs Health*, 2006. 29: 399.
<https://www.ncbi.nlm.nih.gov/pubmed/16977640>
52. Leserman, J. Sexual abuse history: prevalence, health effects, mediators, and psychological treatment. *Psychosom Med*, 2005. 67: 906.
<https://www.ncbi.nlm.nih.gov/pubmed/16314595>
53. Hu, J.C., *et al.* The association of abuse and symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome: results from the Boston Area Community Health survey. *J Gen Intern Med*, 2007. 22: 1532.
<https://www.ncbi.nlm.nih.gov/pubmed/17763912>
54. Linley, J.E., *et al.* Understanding inflammatory pain: ion channels contributing to acute and chronic nociception. *Pflugers Arch*, 2010. 459: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/20162302>
55. Nickel, J.C., *et al.* Prevalence and impact of bacteriuria and/or urinary tract infection in interstitial cystitis/painful bladder syndrome. *Urology*, 2010. 76: 799.
<https://www.ncbi.nlm.nih.gov/pubmed/20573386>

56. Tripp, D.A., *et al.* Sexual functioning, catastrophizing, depression, and pain, as predictors of quality of life in women with interstitial cystitis/painful bladder syndrome. *Urology*, 2009. 73: 987.
<https://www.ncbi.nlm.nih.gov/pubmed/19394494>
57. Tripp, D.A., *et al.* Catastrophizing and pain-contingent rest predict patient adjustment in men with chronic prostatitis/chronic pelvic pain syndrome. *J Pain*, 2006. 7: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/17018330>
58. Whitaker, L.H., *et al.* An Exploratory Study into Objective and Reported Characteristics of Neuropathic Pain in Women with Chronic Pelvic Pain. *PLoS One*, 2016. 11: e0151950.
<https://www.ncbi.nlm.nih.gov/pubmed/27046128>
59. Kutch, J.J., *et al.* Altered resting state neuromotor connectivity in men with chronic prostatitis/chronic pelvic pain syndrome: A MAPP: Research Network Neuroimaging Study. *Neuroimage Clin*, 2015. 8: 493.
<https://www.ncbi.nlm.nih.gov/pubmed/26106574>
60. Abrams, P., *et al.* A new classification is needed for pelvic pain syndromes--are existing terminologies of spurious diagnostic authority bad for patients? *J Urol*, 2006. 175: 1989.
<https://www.ncbi.nlm.nih.gov/pubmed/16697782>
61. Baranowski, A., *et al.*, *Urogenital Pain in Clinical Practice*. 2008, New York.
62. Baranowski, A.P., *et al.* Urogenital pain--time to accept a new approach to phenotyping and, as a consequence, management. *Eur Urol*, 2008. 53: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/17961909>
63. Hanno, P., *et al.* Bladder Pain Syndrome Committee of the International Consultation on Incontinence. *NeuroUrol Urodyn*, 2010. 29: 191.
<https://www.ncbi.nlm.nih.gov/pubmed/20025029>
64. Yoon, B.I., *et al.* Clinical courses following acute bacterial prostatitis. *Prostate International*, 2013. 1: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/24223408>
65. Giamberardino, M.A., *et al.* Viscero-visceral hyperalgesia: characterization in different clinical models. *Pain*, 2010. 151: 307.
<https://www.ncbi.nlm.nih.gov/pubmed/20638177>
66. Wesselmann, U., *et al.* Emerging Therapies and Novel Approaches to Visceral Pain. *Drug Discov Today Ther Strateg*, 2009. 6: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/21243067>
67. Pezet, S., *et al.* Neurotrophins: mediators and modulators of pain. *Annu Rev Neurosci*, 2006. 29: 507.
<https://www.ncbi.nlm.nih.gov/pubmed/16776595>
68. Cervero, F., *et al.* Understanding the signaling and transmission of visceral nociceptive events. *J Neurobiol*, 2004. 61: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/15362152>
69. Nazif, O., *et al.* Neural upregulation in interstitial cystitis. *Urology*, 2007. 69: 24.
<https://www.ncbi.nlm.nih.gov/pubmed/17462476>
70. Melzack, R., *et al.* Central neuroplasticity and pathological pain. *Ann N Y Acad Sci*, 2001. 933: 157.
<https://www.ncbi.nlm.nih.gov/pubmed/12000018>
71. Fulbright, R.K., *et al.* Functional MR imaging of regional brain activation associated with the affective experience of pain. *AJR Am J Roentgenol*, 2001. 177: 1205.
<https://www.ncbi.nlm.nih.gov/pubmed/11641204>
72. Rygh, L.J., *et al.* Cellular memory in spinal nociceptive circuitry. *Scand J Psychol*, 2002. 43: 153.
<https://www.ncbi.nlm.nih.gov/pubmed/12004953>
73. Malykhina, A.P. Neural mechanisms of pelvic organ cross-sensitization. *Neuroscience*, 2007. 149: 660.
<https://www.ncbi.nlm.nih.gov/pubmed/17920206>
74. Grace, V.M. Pitfalls of the medical paradigm in chronic pelvic pain. *Baillieres Best Pract Res Clin Obstet Gynaecol*, 2000. 14: 525.
<https://www.ncbi.nlm.nih.gov/pubmed/10962640>
75. Sharpe, M., *et al.* "Unexplained" somatic symptoms, functional syndromes, and somatization: do we need a paradigm shift? *Ann Intern Med*, 2001. 134: 926.
<https://www.ncbi.nlm.nih.gov/pubmed/11346330>
76. Binik, Y.M. The DSM diagnostic criteria for dyspareunia. *Arch Sex Behav*, 2010. 39: 292.
<https://www.ncbi.nlm.nih.gov/pubmed/19830537>

77. Farmer, M., *et al.* Psychology is from Mars, sexology is from Venus: can they meet on earth? *Canadian Psychology*, 2005. 46: 46.
<https://www.scholars.northwestern.edu/en/publications/psychology-is-from-mars-sexology-is-from-venus-can-they-meet-on-e>
78. Bergeron, S., *et al.* Genital pain in women: Beyond interference with intercourse. *Pain*, 2011. 152: 1223.
<https://www.ncbi.nlm.nih.gov/pubmed/21324589>
79. Davis, S.N., *et al.* Sexual dysfunction and pelvic pain in men: a male sexual pain disorder? *J Sex Marital Ther*, 2009. 35: 182.
<https://www.ncbi.nlm.nih.gov/pubmed/19360518>
80. Leserman, J., *et al.* Identification of diagnostic subtypes of chronic pelvic pain and how subtypes differ in health status and trauma history. *Am J Obstet Gynecol*, 2006. 195: 554.
<https://www.ncbi.nlm.nih.gov/pubmed/16769027>
81. Meltzer-Brody, S., *et al.* Trauma and posttraumatic stress disorder in women with chronic pelvic pain. *Obstet Gynecol*, 2007. 109: 902.
<https://www.ncbi.nlm.nih.gov/pubmed/17400852>
82. Iglesias-Rios, L., *et al.* Depression and Posttraumatic Stress Disorder Among Women with Vulvodynia: Evidence from the Population-Based Woman to Woman Health Study. *J Womens Health*, 2015. 24: 557.
<https://www.ncbi.nlm.nih.gov/pubmed/25950702>
83. Roth, R.S., *et al.* Psychological factors and chronic pelvic pain in women: a comparative study with women with chronic migraine headaches. *Health Care Women Int*, 2011. 32: 746.
<https://www.ncbi.nlm.nih.gov/pubmed/21767098>
84. Souza, P.P., *et al.* Qualitative research as the basis for a biopsychosocial approach to women with chronic pelvic pain. *J Psychosom Obstet Gynaecol*, 2011. 32: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/21919820>
85. Berna, C., *et al.* Presence of mental imagery associated with chronic pelvic pain: a pilot study. *Pain Med*, 2011. 12: 1086.
<https://www.ncbi.nlm.nih.gov/pubmed/21668746>
86. Allaire, C., *et al.*, History-taking, physical examination and psychological assessment. In: Jarrell JF, Vilos GJ (editors) *Consensus guidelines for the management of chronic pelvic pain.*, in *J Obstet Gynaecol Can*. 2005. p. 869.
87. Toye, F., *et al.* A meta-ethnography of patients' experiences of chronic pelvic pain: struggling to construct chronic pelvic pain as 'real'. *J Adv Nurs*, 2014. 70: 2713.
<https://www.ncbi.nlm.nih.gov/pubmed/25081990>
88. Heinberg, L.J., *et al.* Psychological factors in pelvic/urogenital pain: the influence of site of pain versus sex. *Pain*, 2004. 108: 88.
<https://www.ncbi.nlm.nih.gov/pubmed/15109511>
89. Awad, S.A., *et al.* Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women. *Br J Urol*, 1998. 81: 569.
<https://www.ncbi.nlm.nih.gov/pubmed/9598629>
90. Vecchiet, L., *et al.* Referred Muscle Pain: Clinical and Pathophysiologic Aspects. *Curr Rev Pain*, 1999. 3: 489.
<https://www.ncbi.nlm.nih.gov/pubmed/10998708>
91. Slocumb, J.C. Neurological factors in chronic pelvic pain: trigger points and the abdominal pelvic pain syndrome. *Am J Obstet Gynecol*, 1984. 149: 536.
<https://www.ncbi.nlm.nih.gov/pubmed/6234807>
92. Barry, M.J., *et al.* Overlap of different urological symptom complexes in a racially and ethnically diverse, community-based population of men and women. *BJU Int*, 2008. 101: 45.
<https://www.ncbi.nlm.nih.gov/pubmed/17868419>
93. Roberts, R.O., *et al.* Low agreement between previous physician diagnosed prostatitis and national institutes of health chronic prostatitis symptom index pain measures. *J Urol*, 2004. 171: 279.
<https://www.ncbi.nlm.nih.gov/pubmed/14665894>
94. Krieger, J.N., *et al.* Epidemiology of prostatitis. *Int J Antimicrob Agents*, 2008. 31 Suppl 1: S85.
<https://www.ncbi.nlm.nih.gov/pubmed/>
95. Mehik, A., *et al.* Epidemiology of prostatitis in Finnish men: a population-based cross-sectional study. *BJU Int*, 2000. 86: 443.
<https://www.ncbi.nlm.nih.gov/pubmed/18164907>

96. Bade, J.J., *et al.* Interstitial cystitis in The Netherlands: prevalence, diagnostic criteria and therapeutic preferences. *J Urol*, 1995. 154: 2035.
<https://www.ncbi.nlm.nih.gov/pubmed/10971269>
97. Burkman, R.T. Chronic pelvic pain of bladder origin: epidemiology, pathogenesis and quality of life. *J Reprod Med*, 2004. 49: 225.
<https://www.ncbi.nlm.nih.gov/pubmed/15088860>
98. Curhan, G.C., *et al.* Epidemiology of interstitial cystitis: a population based study. *J Urol*, 1999. 161: 549.
<https://www.ncbi.nlm.nih.gov/pubmed/9915446>
99. Held, P., *et al.*, Interstitial Cystitis. Epidemiology of interstitial cystitis. In: Hanno PM, Staskin DR, Krane RJ, Wein AJ, eds. 1990, Springer Verlag: London.
100. Jones, C., *et al.* Prevalence of interstitial cystitis in the United States. *Proc Am Urol Ass J Urol*, 1994. 151 (Suppl). [No abstract available]
101. Leppilahti, M., *et al.* Prevalence of clinically confirmed interstitial cystitis in women: a population based study in Finland. *J Urol*, 2005. 174: 581.
<https://www.ncbi.nlm.nih.gov/pubmed/16006902>
102. Oravisto, K.J. Epidemiology of interstitial cystitis. *Ann Chir Gynaecol Fenn*, 1975. 64: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/971677>
103. Parsons, C.L., *et al.* Prevalence of interstitial cystitis in young women. *Urology*, 2004. 64: 866.
<https://www.ncbi.nlm.nih.gov/pubmed/15533465>
104. Roberts, R.O., *et al.* Incidence of physician-diagnosed interstitial cystitis in Olmsted County: a community-based study. *BJU Int*, 2003. 91: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/12581000>
105. Temml, C., *et al.* Prevalence and correlates for interstitial cystitis symptoms in women participating in a health screening project. *Eur Urol*, 2007. 51: 803.
<https://www.ncbi.nlm.nih.gov/pubmed/16979286>
106. Greenberg, E., *et al.* Transurethral resection of Hunner's ulcer. *J Urol*, 1974. 111: 764.
<https://www.ncbi.nlm.nih.gov/pubmed/4830879>
107. Hand, J.R. Interstitial cystitis; report of 223 cases (204 women and 19 men). *J Urol*, 1949. 61: 291.
<https://www.ncbi.nlm.nih.gov/pubmed/18111850>
108. Koziol, J.A. Epidemiology of interstitial cystitis. *Urol Clin North Am*, 1994. 21: 7.
<https://www.ncbi.nlm.nih.gov/pubmed/8284848>
109. Berry, S.H., *et al.* Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. *J Urol*, 2011. 186: 540.
<https://www.ncbi.nlm.nih.gov/pubmed/21683389>
110. Song, Y., *et al.* Prevalence and correlates of painful bladder syndrome symptoms in Fuzhou Chinese women. *Neurourol Urodyn*, 2009. 28: 22.
<https://www.ncbi.nlm.nih.gov/pubmed/18671294>
111. Koziol, J.A., *et al.* Discrimination between the ulcerous and the nonulcerous forms of interstitial cystitis by noninvasive findings. *J Urol*, 1996. 155: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/7490906>
112. Messing, E.M., *et al.* Interstitial cystitis: early diagnosis, pathology, and treatment. *Urology*, 1978. 12: 381.
<https://www.ncbi.nlm.nih.gov/pubmed/213864>
113. Parsons, C. Interstitial cystitis: clinical manifestations and diagnostic criteria in over 200 cases. *Neurourol Urodyn*, 1990. 9.
<http://onlinelibrary.wiley.com/doi/10.1002/nau.1930090302/abstract>
114. Peeker, R., *et al.* Toward a precise definition of interstitial cystitis: further evidence of differences in classic and nonulcer disease. *J Urol*, 2002. 167: 2470.
<https://www.ncbi.nlm.nih.gov/pubmed/11992059>
115. Smith, C.P., *et al.* Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. *Urology*, 2004. 64: 871.
<https://www.ncbi.nlm.nih.gov/pubmed/15533466>
116. Mattox, T.F. Interstitial cystitis in adolescents and children: a review. *J Pediatr Adolesc Gynecol*, 2004. 17: 7.
<https://www.ncbi.nlm.nih.gov/pubmed/15010032>
117. Berghuis, J.P., *et al.* Psychological and physical factors involved in chronic idiopathic prostatitis. *J Psychosom Res*, 1996. 41: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/8971661>

118. Jacobsen, S.J., *et al.* Frequency of sexual activity and prostatic health: fact or fairy tale? *Urology*, 2003. 61: 348.
<https://www.ncbi.nlm.nih.gov/pubmed/12597946>
119. Lee, S.W., *et al.* Adverse impact of sexual dysfunction in chronic prostatitis/chronic pelvic pain syndrome. *Urology*, 2008. 71: 79.
<https://www.ncbi.nlm.nih.gov/pubmed/18242370>
120. Liang, C.Z., *et al.* Prevalence of sexual dysfunction in Chinese men with chronic prostatitis. *BJU Int*, 2004. 93: 568.
<https://www.ncbi.nlm.nih.gov/pubmed/15008731>
121. Bartoletti, R., *et al.* Prevalence, incidence estimation, risk factors and characterization of chronic prostatitis/chronic pelvic pain syndrome in urological hospital outpatients in Italy: results of a multicenter case-control observational study. *J Urol*, 2007. 178: 2411.
<https://www.ncbi.nlm.nih.gov/pubmed/17937946>
122. Gonen, M., *et al.* Prevalence of premature ejaculation in Turkish men with chronic pelvic pain syndrome. *J Androl*, 2005. 26: 601.
<https://www.ncbi.nlm.nih.gov/pubmed/16088036>
123. Mehik, A., *et al.* Fears, sexual disturbances and personality features in men with prostatitis: a population-based cross-sectional study in Finland. *BJU Int*, 2001. 88: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/11446842>
124. O'Leary, M.P., *et al.* A brief male sexual function inventory for urology. *Urology*, 1995. 46: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/7495124>
125. Weidner, W., *et al.* Acute bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: andrological implications. *Andrologia*, 2008. 40: 105.
<https://www.ncbi.nlm.nih.gov/pubmed/18336460>
126. van Ophoven, A., *et al.* Safety and efficacy of hyperbaric oxygen therapy for the treatment of interstitial cystitis: a randomized, sham controlled, double-blind trial. *J Urol*, 2006. 176: 1442.
<https://www.ncbi.nlm.nih.gov/pubmed/16952654>
127. Rosen, R.C., *et al.* The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*, 1997. 49: 822.
<https://www.ncbi.nlm.nih.gov/pubmed/9187685>
128. Anderson, R.U., *et al.* Sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: improvement after trigger point release and paradoxical relaxation training. *J Urol*, 2006. 176: 1534.
<https://www.ncbi.nlm.nih.gov/pubmed/16952676>
129. Trinchieri, A., *et al.* Prevalence of sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome. *Arch Ital Urol Androl*, 2007. 79: 67.
<https://www.ncbi.nlm.nih.gov/pubmed/17695411>
130. Zondervan, K.T., *et al.* The prevalence of chronic pelvic pain in women in the United Kingdom: a systematic review. *Br J Obstet Gynaecol*, 1998. 105: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/9442169>
131. Grace, V., *et al.* Chronic pelvic pain in women in New Zealand: comparative well-being, comorbidity, and impact on work and other activities. *Health Care Women Int*, 2006. 27: 585.
<https://www.ncbi.nlm.nih.gov/pubmed/16844672>
132. Pitts, M.K., *et al.* Prevalence and correlates of three types of pelvic pain in a nationally representative sample of Australian women. *Med J Aust*, 2008. 189: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/18673099>
133. Verit, F.F., *et al.* The prevalence of sexual dysfunction and associated risk factors in women with chronic pelvic pain: a cross-sectional study. *Arch Gynecol Obstet*, 2006. 274: 297.
<https://www.ncbi.nlm.nih.gov/pubmed/16705463>
134. Wheeler, M.A., *et al.* Effect of long-term oral L-arginine on the nitric oxide synthase pathway in the urine from patients with interstitial cystitis. *J Urol*, 1997. 158: 2045.
<https://www.ncbi.nlm.nih.gov/pubmed/9366309>
135. Florido, J., *et al.* Sexual behavior and findings on laparoscopy or laparotomy in women with severe chronic pelvic pain. *Eur J Obstet Gynecol Reprod Biol*, 2008. 139: 233.
<https://www.ncbi.nlm.nih.gov/pubmed/18403089>
136. Phillips, N.A. The clinical evaluation of dyspareunia. *Int J Impot Res*, 1998. 10 Suppl 2: S117.
<https://www.ncbi.nlm.nih.gov/pubmed/9647973>
137. Ambler, N., *et al.* Sexual difficulties of chronic pain patients. *Clin J Pain*, 2001. 17: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/11444715>

138. Loving, S., *et al.* Pelvic floor muscle dysfunctions are prevalent in female chronic pelvic pain: A cross-sectional population-based study. *Eur J Pain*, 2014. 18: 1259.
<https://www.ncbi.nlm.nih.gov/pubmed/24700500>
139. Chiarioni, G., *et al.* Biofeedback is superior to electrogalvanic stimulation and massage for treatment of levator ani syndrome. *Gastroenterology*, 2010. 138: 1321.
<https://www.ncbi.nlm.nih.gov/pubmed/20044997>
140. Zermann, D., *et al.* Chronic prostatitis: a myofascial pain syndrome? *Infect Urol*, 1999. 12: 84.
<https://www.prostatitis.org/myofascial.html>
141. Shoskes, D.A., *et al.* Muscle tenderness in men with chronic prostatitis/chronic pelvic pain syndrome: the chronic prostatitis cohort study. *J Urol*, 2008. 179: 556.
<https://www.ncbi.nlm.nih.gov/pubmed/18082223>
142. Peters, K.M., *et al.* Prevalence of pelvic floor dysfunction in patients with interstitial cystitis. *Urology*, 2007. 70: 16.
<https://www.ncbi.nlm.nih.gov/pubmed/17656199>
143. Reissing, E.D., *et al.* Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. *J Psychosom Obstet Gynaecol*, 2005. 26: 107.
<https://www.ncbi.nlm.nih.gov/pubmed/16050536>
144. Nickel, J., *et al.* Management of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome who have failed traditional management. *Rev Urol*, 2007. 9: 63.
<https://www.ncbi.nlm.nih.gov/pubmed/17592539>
145. Peters, K.M., *et al.* Childhood symptoms and events in women with interstitial cystitis/painful bladder syndrome. *Urology*, 2009. 73: 258.
<https://www.ncbi.nlm.nih.gov/pubmed/19036420>
146. Rudick, C.N., *et al.* O-antigen modulates infection-induced pain states. *PLoS One*, 2012. 7: e41273.
<https://www.ncbi.nlm.nih.gov/pubmed/22899994>
147. Richter, B., *et al.* YKL-40 and mast cells are associated with detrusor fibrosis in patients diagnosed with bladder pain syndrome/interstitial cystitis according to the 2008 criteria of the European Society for the Study of Interstitial Cystitis. *Histopathology*, 2010. 57: 371.
<https://www.ncbi.nlm.nih.gov/pubmed/20840668>
148. Dundore, P.A., *et al.* Mast cell counts are not useful in the diagnosis of nonulcerative interstitial cystitis. *J Urol*, 1996. 155: 885.
<https://www.ncbi.nlm.nih.gov/pubmed/8583599>
149. Peeker, R., *et al.* Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. *J Urol*, 2000. 163: 1009.
<https://www.ncbi.nlm.nih.gov/pubmed/10688040>
150. Anderstrom, C.R., *et al.* Scanning electron microscopic findings in interstitial cystitis. *Br J Urol*, 1989. 63: 270.
<https://www.ncbi.nlm.nih.gov/pubmed/2702424>
151. Johansson, S.L., *et al.* Clinical features and spectrum of light microscopic changes in interstitial cystitis. *J Urol*, 1990. 143: 1118.
<https://www.ncbi.nlm.nih.gov/pubmed/2342171>
152. Lin, X.C., *et al.* Caveolin-1 may participate in the pathogenesis of bladder pain syndrome/interstitial cystitis. *Urol Int*, 2011. 86: 334.
<https://www.ncbi.nlm.nih.gov/pubmed/21335944>
153. Logadottir, Y.R., *et al.* Intravesical nitric oxide production discriminates between classic and nonulcer interstitial cystitis. *J Urol*, 2004. 171: 1148.
<https://www.ncbi.nlm.nih.gov/pubmed/14767289>
154. Lokeshwar, V.B., *et al.* Urinary uronate and sulfated glycosaminoglycan levels: markers for interstitial cystitis severity. *J Urol*, 2005. 174: 344.
<https://www.ncbi.nlm.nih.gov/pubmed/15947687>
155. Parsons, C.L., *et al.* Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol*, 1991. 145: 732.
<https://www.ncbi.nlm.nih.gov/pubmed/2005689>
156. Parsons, C.L., *et al.* Successful therapy of interstitial cystitis with pentosanpolysulfate. *J Urol*, 1987. 138: 513.
<https://www.ncbi.nlm.nih.gov/pubmed/2442417>
157. Sanchez-Freire, V., *et al.* Acid-sensing channels in human bladder: expression, function and alterations during bladder pain syndrome. *J Urol*, 2011. 186: 1509.
<https://www.ncbi.nlm.nih.gov/pubmed/21855903>

158. Hang, L., *et al.* Cytokine repertoire of epithelial cells lining the human urinary tract. *J Urol*, 1998. 159: 2185.
<https://www.ncbi.nlm.nih.gov/pubmed/9598567>
159. Parsons, C.L., *et al.* Cyto-injury factors in urine: a possible mechanism for the development of interstitial cystitis. *J Urol*, 2000. 164: 1381.
<https://www.ncbi.nlm.nih.gov/pubmed/10992419>
160. Chelimsky, G., *et al.* Autonomic Testing in Women with Chronic Pelvic Pain. *J Urol*, 2016. 196: 429.
<https://www.ncbi.nlm.nih.gov/pubmed/27026035>
161. Charrua, A., *et al.* Can the adrenergic system be implicated in the pathophysiology of bladder pain syndrome/interstitial cystitis? A clinical and experimental study. *Neurourol Urodyn*, 2015. 34: 489.
<https://www.ncbi.nlm.nih.gov/pubmed/24375689>
162. Alagiri, M., *et al.* Interstitial cystitis: unexplained associations with other chronic disease and pain syndromes. *Urology*, 1997. 49: 52.
<https://www.ncbi.nlm.nih.gov/pubmed/9146002>
163. Buffington, C.A. Comorbidity of interstitial cystitis with other unexplained clinical conditions. *J Urol*, 2004. 172: 1242.
<https://www.ncbi.nlm.nih.gov/pubmed/15371816>
164. Clauw, D.J., *et al.* The relationship between fibromyalgia and interstitial cystitis. *J Psychiatr Res*, 1997. 31: 125.
<https://www.ncbi.nlm.nih.gov/pubmed/9201654>
165. Erickson, D.R., *et al.* Nonbladder related symptoms in patients with interstitial cystitis. *J Urol*, 2001. 166: 557.
<https://www.ncbi.nlm.nih.gov/pubmed/11458068>
166. Warren, J., *et al.* Fishbein/interstitial cystitis association (ICA) survey of interstitial cystitis among family members of ICA members: preliminary analysis. *Urology*, 2001. 57: 126.
<https://www.ncbi.nlm.nih.gov/pubmed/11378121>
167. Warren, J.W., *et al.* Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. *Urology*, 2009. 73: 52.
<https://www.ncbi.nlm.nih.gov/pubmed/18995888>
168. Weissman, M., *et al.* Interstitial Cystitis and Panic Disorder - A Potential Genetic Syndrome. *Arch Gen Psych*, 2004. 61.
<https://www.ncbi.nlm.nih.gov/pubmed/14993115>
169. Warren, J.W., *et al.* Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. *Urology*, 2011. 77: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/21295246>
170. Peters, K.M., *et al.* Are ulcerative and nonulcerative interstitial cystitis/painful bladder syndrome 2 distinct diseases? A study of coexisting conditions. *Urology*, 2011. 78: 301.
<https://www.ncbi.nlm.nih.gov/pubmed/21703668>
171. Rab, M., *et al.* Anatomic variability of the ilioinguinal and genitofemoral nerve: implications for the treatment of groin pain. *Plast Reconstr Surg*, 2001. 108: 1618.
<https://www.ncbi.nlm.nih.gov/pubmed/11711938>
172. Eklund, A., *et al.* Chronic pain 5 years after randomized comparison of laparoscopic and Lichtenstein inguinal hernia repair. *Br J Surg*, 2010. 97: 600.
<https://www.ncbi.nlm.nih.gov/pubmed/20186889>
173. Nariculum, J., *et al.* A review of the efficacy of surgical treatment for and pathological changes in patients with chronic scrotal pain. *BJU Int*, 2007. 99: 1091.
<https://www.ncbi.nlm.nih.gov/pubmed/17244279>
174. Manikandan, R., *et al.* Early and late morbidity after vasectomy: a comparison of chronic scrotal pain at 1 and 10 years. *BJU Int*, 2004. 93: 571.
<https://www.ncbi.nlm.nih.gov/pubmed/15008732>
175. Leslie, T.A., *et al.* The incidence of chronic scrotal pain after vasectomy: a prospective audit. *BJU Int*, 2007. 100: 1330.
<https://www.ncbi.nlm.nih.gov/pubmed/17850378>
176. Hallen, M., *et al.* Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: long-term follow-up of a randomized controlled trial. *Surgery*, 2008. 143: 313.
<https://www.ncbi.nlm.nih.gov/pubmed/18291251>
177. Grant, A.M., *et al.* Five-year follow-up of a randomized trial to assess pain and numbness after laparoscopic or open repair of groin hernia. *Br J Surg*, 2004. 91: 1570.
<https://www.ncbi.nlm.nih.gov/pubmed/15515112>

178. Parsons, C.L. The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain. *BJU Int*, 2011. 107: 370.
<https://www.ncbi.nlm.nih.gov/pubmed/21176078>
179. Parsons, C.L., *et al.* Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. *Urology*, 2001. 57: 428.
<https://www.ncbi.nlm.nih.gov/pubmed/11248610>
180. Kaur, H., *et al.* Urethral pain syndrome and its management. *Obstet Gynecol Surv*, 2007. 62: 348.
<https://www.ncbi.nlm.nih.gov/pubmed/17425813>
181. Gurel, H., *et al.* Urethral syndrome and associated risk factors related to obstetrics and gynecology. *Eur J Obstet Gynecol Reprod Biol*, 1999. 83: 5.
<https://www.ncbi.nlm.nih.gov/pubmed/10221602>
182. Hahn, L. Treatment of ilioinguinal nerve entrapment - a randomized controlled trial. *Acta Obstet Gynecol Scand*, 2011. 90: 955.
<https://www.ncbi.nlm.nih.gov/pubmed/21615360>
183. Antolak, S.J., Jr., *et al.* Anatomical basis of chronic pelvic pain syndrome: the ischial spine and pudendal nerve entrapment. *Med Hypotheses*, 2002. 59: 349.
<https://www.ncbi.nlm.nih.gov/pubmed/12208168>
184. Mahakkanukrauh, P., *et al.* Anatomical study of the pudendal nerve adjacent to the sacrospinous ligament. *Clin Anat*, 2005. 18: 200.
<https://www.ncbi.nlm.nih.gov/pubmed/15768420>
185. Labat, J.J., *et al.* Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). *Neurourol Urodyn*, 2008. 27: 306.
<https://www.ncbi.nlm.nih.gov/pubmed/17828787>
186. Robert, R., *et al.* Anatomic basis of chronic perineal pain: role of the pudendal nerve. *Surg Radiol Anat*, 1998. 20: 93.
<https://www.ncbi.nlm.nih.gov/pubmed/9658526>
187. Shafik, A. Pudendal canal syndrome as a cause of vulvodynia and its treatment by pudendal nerve decompression. *Eur J Obstet Gynecol Reprod Biol*, 1998. 80: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/9846672>
188. Amarenco, G., *et al.* Electrophysiological analysis of pudendal neuropathy following traction. *Muscle Nerve*, 2001. 24: 116.
<https://www.ncbi.nlm.nih.gov/pubmed/11150974>
189. Goldet, R., *et al.* [Traction on the orthopedic table and pudendal nerve injury. Importance of electrophysiologic examination]. *Rev Chir Orthop Reparatrice Appar Mot*, 1998. 84: 523.
<https://www.ncbi.nlm.nih.gov/pubmed/9846326>
190. Alevizon, S.J., *et al.* Sacrospinous colpopexy: management of postoperative pudendal nerve entrapment. *Obstet Gynecol*, 1996. 88: 713.
<https://www.ncbi.nlm.nih.gov/pubmed/8841264>
191. Fisher, H.W., *et al.* Nerve injury locations during retropubic sling procedures. *Int Urogynecol J*, 2011. 22: 439.
<https://www.ncbi.nlm.nih.gov/pubmed/21060989>
192. Moszkowicz, D., *et al.* Where does pelvic nerve injury occur during rectal surgery for cancer? *Colorectal Dis*, 2011. 13: 1326.
<https://www.ncbi.nlm.nih.gov/pubmed/20718836>
193. Ashton-Miller, J.A., *et al.* Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci*, 2007. 1101: 266.
<https://www.ncbi.nlm.nih.gov/pubmed/17416924>
194. Amarenco, G., *et al.* [Perineal neuropathy due to stretching and urinary incontinence. Physiopathology, diagnosis and therapeutic implications]. *Ann Urol (Paris)*, 1990. 24: 463.
<https://www.ncbi.nlm.nih.gov/pubmed/2176777>
195. Fleming, M., *et al.* Sexuality and chronic pain. *J Sex Educ Ther*, 2001. 26: 204.
<http://www.tandfonline.com/doi/abs/10.1080/01614576.2001.11074415>
196. Maruta, T., *et al.* Chronic pain patients and spouses: marital and sexual adjustment. *Mayo Clin Proc*, 1981. 56: 307.
<https://www.ncbi.nlm.nih.gov/pubmed/7230895>
197. Muller, A., *et al.* Sexual dysfunction in the patient with prostatitis. *Curr Opin Urol*, 2005. 15: 404.
<https://www.ncbi.nlm.nih.gov/pubmed/16205492>

198. Chen, X., *et al.* The effect of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) on erectile function: A systematic review and meta-analysis. *PLoS ONE*, 2015. 10 (10) (no pagination).
<https://www.ncbi.nlm.nih.gov/pubmed/26509575>
199. Tripp, D.A., *et al.* Prevalence, symptom impact and predictors of chronic prostatitis-like symptoms in Canadian males aged 16-19 years. *BJU Int*, 2009. 103: 1080.
<https://www.ncbi.nlm.nih.gov/pubmed/19007369>
200. Egan, K.J., *et al.* Psychological problems in chronic prostatitis patients with pain. *Clin J Pain*, 1994. 10: 218.
<https://www.ncbi.nlm.nih.gov/pubmed/7833580>
201. Smith, K.B., *et al.* Sexual and relationship functioning in men with chronic prostatitis/chronic pelvic pain syndrome and their partners. *Arch Sex Behav*, 2007. 36: 301.
<https://www.ncbi.nlm.nih.gov/pubmed/17186130>
202. Gunter, J. Chronic pelvic pain: an integrated approach to diagnosis and treatment. *Obstet Gynecol Surv*, 2003. 58: 615.
<https://www.ncbi.nlm.nih.gov/pubmed/12972837>
203. Latthe, P., *et al.* WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. *BMC Public Health*, 2006. 6: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/16824213>
204. Pearce, C., *et al.* A multidisciplinary approach to self care in chronic pelvic pain. *Br J Nurs*, 2007. 16: 82.
<https://www.ncbi.nlm.nih.gov/pubmed/17353816>
205. ter Kuile, M.M., *et al.* Sexual functioning in women with chronic pelvic pain: the role of anxiety and depression. *J Sex Med*, 2010. 7: 1901.
<https://www.ncbi.nlm.nih.gov/pubmed/19678881>
206. Fry, R.P., *et al.* Patients' illness models in chronic pelvic pain. *Psychother Psychosom*, 1991. 55: 158.
<https://www.ncbi.nlm.nih.gov/pubmed/1891563>
207. Collett, B.J., *et al.* A comparative study of women with chronic pelvic pain, chronic nonpelvic pain and those with no history of pain attending general practitioners. *Br J Obstet Gynaecol*, 1998. 105: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/9442168>
208. McCabe, M.P., *et al.* Intercorrelations among general arousability, emerging and current sexual desire, and severity of sexual dysfunction in women. *Psychol Rep*, 1989. 65: 147.
<https://www.ncbi.nlm.nih.gov/pubmed/2780925>
209. Flor, H., *et al.* The role of spouse reinforcement, perceived pain, and activity levels of chronic pain patients. *J Psychosom Res*, 1987. 31: 251.
<https://www.ncbi.nlm.nih.gov/pubmed/3585827>
210. Paice, J. Sexuality and chronic pain. *Am J Nurs*, 2003. 103: 87.
<https://www.ncbi.nlm.nih.gov/pubmed/12544064>
211. Verit, F.F., *et al.* Validation of the female sexual function index in women with chronic pelvic pain. *J Sex Med*, 2007. 4: 1635.
<https://www.ncbi.nlm.nih.gov/pubmed/17888066>
212. Hetrick, D.C., *et al.* Musculoskeletal dysfunction in men with chronic pelvic pain syndrome type III: a case-control study. *J Urol*, 2003. 170: 828.
<https://www.ncbi.nlm.nih.gov/pubmed/12913709>
213. Clemens, J.Q., *et al.* Biofeedback, pelvic floor re-education, and bladder training for male chronic pelvic pain syndrome. *Urology*, 2000. 56: 951.
<https://www.ncbi.nlm.nih.gov/pubmed/11113739>
214. Ishigooka, M., *et al.* Similarity of distributions of spinal c-Fos and plasma extravasation after acute chemical irritation of the bladder and the prostate. *J Urol*, 2000. 164: 1751.
<https://www.ncbi.nlm.nih.gov/pubmed/11025764>
215. Zondervan, K.T., *et al.* Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database. *Br J Obstet Gynaecol*, 1999. 106: 1149.
<https://www.ncbi.nlm.nih.gov/pubmed/10549959>
216. Drossman, D.A., *et al.* U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci*, 1993. 38: 1569.
<https://www.ncbi.nlm.nih.gov/pubmed/8359066>
217. Prior, A., *et al.* Gynaecological consultation in patients with the irritable bowel syndrome. *Gut*, 1989. 30: 996.
<https://www.ncbi.nlm.nih.gov/pubmed/2759494>

218. Longstreth, G.F., *et al.* Irritable bowel syndrome in women having diagnostic laparoscopy or hysterectomy. Relation to gynecologic features and outcome. *Dig Dis Sci*, 1990. 35: 1285.
<https://www.ncbi.nlm.nih.gov/pubmed/2145139>
219. Sperber, A.D., *et al.* Development of abdominal pain and IBS following gynecological surgery: a prospective, controlled study. *Gastroenterology*, 2008. 134: 75.
<https://www.ncbi.nlm.nih.gov/pubmed/18166349>
220. Monnikes, H. Quality of life in patients with irritable bowel syndrome. *J Clin Gastroenterol*, 2011. 45 Suppl: S98.
<https://www.ncbi.nlm.nih.gov/pubmed/21666428>
221. Canavan, C., *et al.* Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther*, 2014. 40: 1023.
<https://www.ncbi.nlm.nih.gov/pubmed/25199904>
222. Morgan, C.J., *et al.* Ketamine use: a review. *Addiction*, 2012. 107: 27.
<https://www.ncbi.nlm.nih.gov/pubmed/21777321>
223. Lorencatto, C., *et al.* Depression in women with endometriosis with and without chronic pelvic pain. *Acta Obstet Gynecol Scand*, 2006. 85: 88.
<https://www.ncbi.nlm.nih.gov/pubmed/16521687>
224. Pincus, T., *et al.* Models and measurements of depression in chronic pain. *J Psychosom Res*, 1999. 47: 211.
<https://www.ncbi.nlm.nih.gov/pubmed/10576470>
225. Stones, R.W., *et al.* Psychosocial and economic impact of chronic pelvic pain. *Baillieres Best Pract Res Clin Obstet Gynaecol*, 2000. 14: 415.
<https://www.ncbi.nlm.nih.gov/pubmed/10962635>
226. Howard, F.M. Chronic pelvic pain. *Obstet Gynecol*, 2003. 101: 594.
<https://www.ncbi.nlm.nih.gov/pubmed/12636968>
227. Fitzgerald, M.P., *et al.* Beyond the lower urinary tract: the association of urologic and sexual symptoms with common illnesses. *Eur Urol*, 2007. 52: 407.
<https://www.ncbi.nlm.nih.gov/pubmed/17382458>
228. Davis, S.N., *et al.* Is a sexual dysfunction domain important for quality of life in men with urological chronic pelvic pain syndrome? Signs "UPOINT" to yes. *J Urol*, 2013. 189: 146.
<https://www.ncbi.nlm.nih.gov/pubmed/23164384>
229. Cleeland, C.S. The Brief Pain Inventory User Guide. 2009.
https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf
230. Turk, D.C., *et al.* Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 2003. 106: 337.
<https://www.ncbi.nlm.nih.gov/pubmed/14659516>
231. Bullock, A.D., *et al.* Experimental autoimmune cystitis: a potential murine model for ulcerative interstitial cystitis. *J Urol*, 1992. 148: 1951.
<https://www.ncbi.nlm.nih.gov/pubmed/1433651>
232. Dodd, L.G., *et al.* Cytologic examination of urine from patients with interstitial cystitis. *Acta Cytol*, 1998. 42: 923.
<https://www.ncbi.nlm.nih.gov/pubmed/9684578>
233. Erickson, D.R., *et al.* Interstitial cystitis. *Int Urogynecol J Pelvic Floor Dysfunct*, 1998. 9: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/9745978>
234. Fall, M., *et al.* Chronic interstitial cystitis: a heterogeneous syndrome. *J Urol*, 1987. 137: 35.
<https://www.ncbi.nlm.nih.gov/pubmed/3795363>
235. Warren, J.W., *et al.* Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. *Urology*, 2008. 71: 444.
<https://www.ncbi.nlm.nih.gov/pubmed/18342184>
236. Bharucha, A.E., *et al.* Functional anorectal disorders. *Gastroenterology*, 2006. 130: 1510.
<https://www.ncbi.nlm.nih.gov/pubmed/16678564>
237. McNaughton Collins, M., *et al.* Quality of life is impaired in men with chronic prostatitis: the Chronic Prostatitis Collaborative Research Network. *J Gen Intern Med*, 2001. 16: 656.
<https://www.ncbi.nlm.nih.gov/pubmed/11679032>
238. Wenninger, K., *et al.* Sickness impact of chronic nonbacterial prostatitis and its correlates. *J Urol*, 1996. 155: 965.
<https://www.ncbi.nlm.nih.gov/pubmed/8583619>

239. Gerlinger, C., *et al.* Defining a minimal clinically important difference for endometriosis-associated pelvic pain measured on a visual analog scale: analyses of two placebo-controlled, randomized trials. *Health Qual Life Outcomes*, 2010. 8: 138.
<https://www.ncbi.nlm.nih.gov/pubmed/21106059>
240. Litwin, M.S., *et al.* The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol*, 1999. 162: 369.
<https://www.ncbi.nlm.nih.gov/pubmed/10411041>
241. Mebust, W., *et al.*, Symptom evaluation, quality of life and sexuality. In: 2nd Consultation on Benign Prostatic Hyperplasia (BPH). 1993, Jersey, Channel Islands.
242. Lubeck, D.P., *et al.* Psychometric validation of the O'leary-Sant interstitial cystitis symptom index in a clinical trial of pentosan polysulfate sodium. *Urology*, 2001. 57: 62.
<https://www.ncbi.nlm.nih.gov/pubmed/11378052>
243. Francis, C.Y., *et al.* The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther*, 1997. 11: 395.
<https://www.ncbi.nlm.nih.gov/pubmed/9146781>
244. Spiegel, B.M., *et al.* Characterizing abdominal pain in IBS: guidance for study inclusion criteria, outcome measurement and clinical practice. *Aliment Pharmacol Ther*, 2010. 32: 1192.
<https://www.ncbi.nlm.nih.gov/pubmed/20807217>
245. Slieker-ten Hove, M.C., *et al.* Face validity and reliability of the first digital assessment scheme of pelvic floor muscle function conform the new standardized terminology of the International Continence Society. *Neurourol Urodyn*, 2009. 28: 295.
<https://www.ncbi.nlm.nih.gov/pubmed/19090583>
246. Wyndaele, J.J., *et al.* Reproducibility of digital testing of the pelvic floor muscles in men. *Arch Phys Med Rehabil*, 1996. 77: 1179.
<https://www.ncbi.nlm.nih.gov/pubmed/8931532>
247. Davis, S.N., *et al.* Use of pelvic floor ultrasound to assess pelvic floor muscle function in urological chronic pelvic pain syndrome in men. *J Sex Med*, 2011. 8: 3173.
<https://www.ncbi.nlm.nih.gov/pubmed/21883952>
248. Anderson, R.U., *et al.* Painful myofascial trigger points and pain sites in men with chronic prostatitis/chronic pelvic pain syndrome. *J Urol*, 2009. 182: 2753.
<https://www.ncbi.nlm.nih.gov/pubmed/19837420>
249. Antolak, S.J., Jr., *et al.* Therapeutic pudendal nerve blocks using corticosteroids cure pelvic pain after failure of sacral neuromodulation. *Pain Med*, 2009. 10: 186.
<https://www.ncbi.nlm.nih.gov/pubmed/19222779>
250. Bolandard, F., *et al.* Nerve stimulator guided pudendal nerve blocks. *Can J Anaesth*, 2005. 52: 773; author reply 773.
<https://www.ncbi.nlm.nih.gov/pubmed/16103396>
251. Filler, A.G. Diagnosis and treatment of pudendal nerve entrapment syndrome subtypes: imaging, injections, and minimal access surgery. *Neurosurg Focus*, 2009. 26: E9.
<https://www.ncbi.nlm.nih.gov/pubmed/19323602>
252. Kim, S.H., *et al.* Nerve-stimulator-guided pudendal nerve block by pararectal approach. *Colorectal Dis*, 2012. 14: 611.
<https://www.ncbi.nlm.nih.gov/pubmed/21752174>
253. Kovacs, P., *et al.* New, simple, ultrasound-guided infiltration of the pudendal nerve: ultrasonographic technique. *Dis Colon Rectum*, 2001. 44: 1381.
<https://www.ncbi.nlm.nih.gov/pubmed/11584221>
254. Naja, M.Z., *et al.* Nerve-stimulator-guided repeated pudendal nerve block for treatment of pudendal neuralgia. *Eur J Anaesthesiol*, 2006. 23: 442.
<https://www.ncbi.nlm.nih.gov/pubmed/16573866>
255. Peng, P.W., *et al.* Ultrasound-guided interventional procedures for patients with chronic pelvic pain - a description of techniques and review of literature. *Pain Physician*, 2008. 11: 215.
<https://www.ncbi.nlm.nih.gov/pubmed/18354713>
256. Rigaud, J., *et al.* [Somatic nerve block in the management of chronic pelvic and perineal pain]. *Prog Urol*, 2010. 20: 1072.
<https://www.ncbi.nlm.nih.gov/pubmed/21056387>
257. Romanzi, L. Techniques of pudendal nerve block. *J Sex Med*, 2010. 7: 1716.
<https://www.ncbi.nlm.nih.gov/pubmed/20537059>

258. Thoumas, D., *et al.* Pudendal neuralgia: CT-guided pudendal nerve block technique. *Abdom Imaging*, 1999. 24: 309.
<https://www.ncbi.nlm.nih.gov/pubmed/10227901>
259. Wey, P.F., *et al.* [Nerve stimulator guided pudendal nerve block for postoperative analgesia. An evaluation of professional practice]. *Ann Fr Anesth Reanim*, 2007. 26: 1087.
<https://www.ncbi.nlm.nih.gov/pubmed/17961968>
260. Bates, S.M., *et al.* A prospective, randomized, double-blind trial to evaluate the role of a short reducing course of oral corticosteroid therapy in the treatment of chronic prostatitis/chronic pelvic pain syndrome. *BJU Int*, 2007. 99: 355.
<https://www.ncbi.nlm.nih.gov/pubmed/17313424>
261. Dragoman, M.V. The combined oral contraceptive pill -- recent developments, risks and benefits. *Best Pract Res Clin Obstet Gynaecol*, 2014. 28: 825.
<https://www.ncbi.nlm.nih.gov/pubmed/25028259>
262. Ghaly, A. The psychological and physical benefits of pelvic ultrasonography in patients with chronic pelvic pain and negative laparoscopy. A random allocation trial. *J Obstet Gynaecol*, 1994. 14.
<http://www.tandfonline.com/doi/abs/10.3109/01443619409027849?journalCode=ijog20>
263. Nickel, J.C., *et al.* Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. *J Urol*, 2004. 171: 1594.
<https://www.ncbi.nlm.nih.gov/pubmed/15017228>
264. Zhao, W.P., *et al.* Celecoxib reduces symptoms in men with difficult chronic pelvic pain syndrome (Category IIIA). *Braz J Med Biol Res*, 2009. 42: 963.
<https://www.ncbi.nlm.nih.gov/pubmed/19787151>
265. Poldrack, R., *et al.* Scanning the Horizon: challenges and solutions for neuroimaging research. *bioRxiv*, 2016.
<http://biorxiv.org/content/early/2016/08/01/059188>
266. Salomons, T.V., *et al.* The "pain matrix" in pain-free individuals. *JAMA Neurology*, 2016. 73: 755.
<https://www.ncbi.nlm.nih.gov/pubmed/27111250>
267. Meares, E.M., *et al.* Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol*, 1968. 5: 492.
<https://www.ncbi.nlm.nih.gov/pubmed/4870505>
268. Nickel, J.C. The Pre and Post Massage Test (PPMT): a simple screen for prostatitis. *Tech Urol*, 1997. 3: 38.
<https://www.ncbi.nlm.nih.gov/pubmed/9170224>
269. Nickel, J.C., *et al.* How does the pre-massage and post-massage 2-glass test compare to the Meares-Stamey 4-glass test in men with chronic prostatitis/chronic pelvic pain syndrome? *J Urol*, 2006. 176: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/16753385>
270. Nickel, J.C., *et al.* A randomized, placebo controlled, multicenter study to evaluate the safety and efficacy of rofecoxib in the treatment of chronic nonbacterial prostatitis. *J Urol*, 2003. 169: 1401.
<https://www.ncbi.nlm.nih.gov/pubmed/12629372>
271. Howard, F.M. The role of laparoscopy as a diagnostic tool in chronic pelvic pain. *Baillieres Best Pract Res Clin Obstet Gynaecol*, 2000. 14: 467.
<https://www.ncbi.nlm.nih.gov/pubmed/10962637>
272. Jacobson, T.Z., *et al.* Laparoscopic surgery for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev*, 2009: CD001300.
<https://www.ncbi.nlm.nih.gov/pubmed/19821276>
273. Porpora, M.G., *et al.* The role of laparoscopy in the management of pelvic pain in women of reproductive age. *Fertil Steril*, 1997. 68: 765.
<https://www.ncbi.nlm.nih.gov/pubmed/9389799>
274. Seracchioli, R., *et al.* Cystoscopy-assisted laparoscopic resection of extramucosal bladder endometriosis. *J Endourol*, 2002. 16: 663.
<https://www.ncbi.nlm.nih.gov/pubmed/12490020>
275. Wyndaele, J.J., *et al.* Cystoscopy and bladder biopsies in patients with bladder pain syndrome carried out following ESSIC guidelines. *Scand J Urol Nephrol*, 2009. 43: 471.
<https://www.ncbi.nlm.nih.gov/pubmed/>
276. Elcombe, S., *et al.* The psychological effects of laparoscopy on women with chronic pelvic pain. *Psychol Med*, 1997. 27: 1041.
<https://www.ncbi.nlm.nih.gov/pubmed/9300510>

277. Onwude, J.L., *et al.* A randomised trial of photographic reinforcement during postoperative counselling after diagnostic laparoscopy for pelvic pain. *Eur J Obstet Gynecol Reprod Biol*, 2004. 112: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/14687747>
278. Peters, A.A., *et al.* A randomized clinical trial to compare two different approaches in women with chronic pelvic pain. *Obstet Gynecol*, 1991. 77: 740.
<https://www.ncbi.nlm.nih.gov/pubmed/1826544>
279. Cole, E.E., *et al.* Are patient symptoms predictive of the diagnostic and/or therapeutic value of hydrodistention? *Neurourol Urodyn*, 2005. 24: 638.
<https://www.ncbi.nlm.nih.gov/pubmed/16208660>
280. Lamale, L.M., *et al.* Symptoms and cystoscopic findings in patients with untreated interstitial cystitis. *Urology*, 2006. 67: 242.
<https://www.ncbi.nlm.nih.gov/pubmed/16442603>
281. Ottem, D.P., *et al.* What is the value of cystoscopy with hydrodistension for interstitial cystitis? *Urology*, 2005. 66: 494.
<https://www.ncbi.nlm.nih.gov/pubmed/16140064>
282. Shear, S., *et al.* Development of glomerulations in younger women with interstitial cystitis. *Urology*, 2006. 68: 253.
<https://www.ncbi.nlm.nih.gov/pubmed/16904429>
283. Tamaki, M., *et al.* Possible mechanisms inducing glomerulations in interstitial cystitis: relationship between endoscopic findings and expression of angiogenic growth factors. *J Urol*, 2004. 172: 945.
<https://www.ncbi.nlm.nih.gov/pubmed/15311005>
284. Aihara, K., *et al.* Hydrodistension under local anesthesia for patients with suspected painful bladder syndrome/interstitial cystitis: safety, diagnostic potential and therapeutic efficacy. *Int J Urol*, 2009. 16: 947.
<https://www.ncbi.nlm.nih.gov/pubmed/19817916>
285. Messing, E., *et al.* Associations among cystoscopic findings and symptoms and physical examination findings in women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. *Urology*, 1997. 49: 81.
<https://www.ncbi.nlm.nih.gov/pubmed/9146006>
286. Waxman, J.A., *et al.* Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. *J Urol*, 1998. 160: 1663.
<https://www.ncbi.nlm.nih.gov/pubmed/9783927>
287. Geurts, N., *et al.* Bladder pain syndrome: do the different morphological and cystoscopic features correlate? *Scand J Urol Nephrol*, 2011. 45: 20.
<https://www.ncbi.nlm.nih.gov/pubmed/20846081>
288. Johansson, S.L., *et al.* Pathology of interstitial cystitis. *Urol Clin North Am*, 1994. 21: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/8284845>
289. Wassong, C., *et al.* Radiologic findings of pelvic venous congestion in an adolescent girl with angiographic confirmation and interventional treatment. *Pediatr Radiol*, 2012. 42: 636.
<https://www.ncbi.nlm.nih.gov/pubmed/21912968>
290. Ness, R.B., *et al.* Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. *Am J Obstet Gynecol*, 2002. 186: 929.
<https://www.ncbi.nlm.nih.gov/pubmed/12015517>
291. Corey, L., *et al.* Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med*, 1983. 98: 958.
<https://www.ncbi.nlm.nih.gov/pubmed/6344712>
292. Young, H., *et al.* Screening for treponemal infection by a new enzyme immunoassay. *Genitourin Med*, 1989. 65: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/2666302>
293. Culley, L., *et al.* The social and psychological impact of endometriosis on women's lives: A critical narrative review. *Human Reprod Update*, 2013. 19: 625.
<https://www.ncbi.nlm.nih.gov/pubmed/23884896>
294. Souza, C.A., *et al.* Quality of life associated to chronic pelvic pain is independent of endometriosis diagnosis--a cross-sectional survey. *Health Qual Life Outcomes*, 2011. 9.
295. Barri, P.N., *et al.* Endometriosis-associated infertility: surgery and IVF, a comprehensive therapeutic approach. *Reprod Biomed Online*, 2010. 21: 179.
<https://www.ncbi.nlm.nih.gov/pubmed/21663624>

296. Fauconnier, A., *et al.* Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. *Fertil Steril*, 2002. 78: 719.
<https://www.ncbi.nlm.nih.gov/pubmed/12372446>
297. Vercellini, P., *et al.* The effect of surgery for symptomatic endometriosis: the other side of the story. *Hum Reprod Update*, 2009. 15: 177.
<https://www.ncbi.nlm.nih.gov/pubmed/19136455>
298. Vercellini, P., *et al.* Medical treatment for rectovaginal endometriosis: what is the evidence? *Hum Reprod*, 2009. 24: 2504.
<https://www.ncbi.nlm.nih.gov/pubmed/19574277>
299. Kaminski, P., *et al.* The usefulness of laparoscopy and hysteroscopy in the diagnostics and treatment of infertility. *Neuro Endocrinol Lett*, 2006. 27: 813.
<https://www.ncbi.nlm.nih.gov/pubmed/17187014>
300. Hay-Smith, E.J. Therapeutic ultrasound for postpartum perineal pain and dyspareunia. *Cochrane Database Syst Rev*, 2000: CD000495.
<https://www.ncbi.nlm.nih.gov/pubmed/10796210>
301. Roovers, J.P., *et al.* A randomised controlled trial comparing abdominal and vaginal prolapse surgery: effects on urogenital function. *BJOG*, 2004. 111: 50.
<https://www.ncbi.nlm.nih.gov/pubmed/14687052>
302. Lin, L.L., *et al.* Dyspareunia and chronic pelvic pain after polypropylene mesh augmentation for transvaginal repair of anterior vaginal wall prolapse. *Int Urogynecol J Pelvic Floor Dysfunct*, 2007. 18: 675.
<https://www.ncbi.nlm.nih.gov/pubmed/16988779>
303. Niro, J., *et al.* [Postoperative pain after transvaginal repair of pelvic organ prolapse with or without mesh]. *Gynecol Obstet Fertil*, 2010. 38: 648.
<https://www.ncbi.nlm.nih.gov/pubmed/21030280>
304. Withagen, M.I., *et al.* Risk factors for exposure, pain, and dyspareunia after tension-free vaginal mesh procedure. *Obstet Gynecol*, 2011. 118: 629.
<https://www.ncbi.nlm.nih.gov/pubmed/21860293>
305. Brandt, L.J., *et al.* An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol*, 2009. 104 Suppl 1: S1.
<https://www.ncbi.nlm.nih.gov/pubmed/19521341>
306. Spiller, R., *et al.* Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut*, 2007. 56: 1770.
<https://www.ncbi.nlm.nih.gov/pubmed/17488783>
307. McGowan, L., *et al.* How do you explain a pain that can't be seen?: the narratives of women with chronic pelvic pain and their disengagement with the diagnostic cycle. *Br J Health Psychol*, 2007. 12: 261.
<https://www.ncbi.nlm.nih.gov/pubmed/17456285>
308. European Association of Urology (EAU). EAU Survey: What do you tell your patients?
309. Loving, S., *et al.* Does evidence support physiotherapy management of adult female chronic pelvic pain?. *Scand J Pain*, 2012. 3: 70.
[http://www.scandinavianjournalpain.com/article/S1877-8860\(11\)00153-4/abstract](http://www.scandinavianjournalpain.com/article/S1877-8860(11)00153-4/abstract)
310. Haugstad, G.K., *et al.* Mensendieck somatocognitive therapy as treatment approach to chronic pelvic pain: results of a randomized controlled intervention study. *Am J Obstet Gynecol*, 2006. 194: 1303.
<https://www.ncbi.nlm.nih.gov/pubmed/16647914>
311. FitzGerald, M.P., *et al.* Randomized multicenter feasibility trial of myofascial physical therapy for the treatment of urological chronic pelvic pain syndromes. *J Urol*, 2013. 189: S75.
<https://www.ncbi.nlm.nih.gov/pubmed/23234638>
312. de las Penas, C., *et al.* Manual therapies in myofascial trigger point treatment: a systematic review. *J Bodyw Mov Ther*, 2005. 9: 27.
[http://www.bodyworkmovementtherapies.com/article/S1360-8592\(03\)00106-2/abstract](http://www.bodyworkmovementtherapies.com/article/S1360-8592(03)00106-2/abstract)
313. Tough, E.A., *et al.* Acupuncture and dry needling in the management of myofascial trigger point pain: a systematic review and meta-analysis of randomised controlled trials. *Eur J Pain*, 2009. 13: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/18395479>
314. Cummings, T.M., *et al.* Needling therapies in the management of myofascial trigger point pain: a systematic review. *Arch Phys Med Rehabil*, 2001. 82: 986.
<https://www.ncbi.nlm.nih.gov/pubmed/11441390>

315. Scott, N.A., *et al.* Trigger point injections for chronic non-malignant musculoskeletal pain: a systematic review. *Pain Med*, 2009. 10: 54.
<https://www.ncbi.nlm.nih.gov/pubmed/18992040>
316. Karper, W.B. Exercise effects on interstitial cystitis: two case reports. *Urol Nurs*, 2004. 24: 202.
<https://www.ncbi.nlm.nih.gov/pubmed/15311489>
317. Oyama, I.A., *et al.* Modified Thiele massage as therapeutic intervention for female patients with interstitial cystitis and high-tone pelvic floor dysfunction. *Urology*, 2004. 64: 862.
<https://www.ncbi.nlm.nih.gov/pubmed/15533464>
318. Langford, C.F., *et al.* Levator ani trigger point injections: An underutilized treatment for chronic pelvic pain. *NeuroUrol Urodyn*, 2007. 26: 59.
<https://www.ncbi.nlm.nih.gov/pubmed/17195176>
319. FitzGerald, M.P., *et al.* Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. *J Urol*, 2012. 187: 2113.
<https://www.ncbi.nlm.nih.gov/pubmed/22503015>
320. Kellog-Spadt, S., *et al.*, Role of the female urologist/urogynecologist. In: *Women's sexual function and dysfunction: Study, diagnosis and treatment*. 2006, Taylor and Francis: London.
321. Webster, D.C., *et al.* Use and effectiveness of physical self-care strategies for interstitial cystitis. *Nurse Pract*, 1994. 19: 55.
<https://www.ncbi.nlm.nih.gov/pubmed/2913346>
322. Hayes, R.D., *et al.* What can prevalence studies tell us about female sexual difficulty and dysfunction? *J Sex Med*, 2006. 3: 589.
<https://www.ncbi.nlm.nih.gov/pubmed/16839314>
323. Rosenbaum, T.Y., *et al.* The role of pelvic floor physical therapy in the treatment of pelvic and genital pain-related sexual dysfunction (CME). *J Sex Med*, 2008. 5: 513.
<https://www.ncbi.nlm.nih.gov/pubmed/18304280>
324. Rowe, E., *et al.* A prospective, randomized, placebo controlled, double-blind study of pelvic electromagnetic therapy for the treatment of chronic pelvic pain syndrome with 1 year of followup. *J Urol*, 2005. 173: 2044.
<https://www.ncbi.nlm.nih.gov/pubmed/15879822>
325. Kastner, C., *et al.* Cooled transurethral microwave thermotherapy for intractable chronic prostatitis--results of a pilot study after 1 year. *Urology*, 2004. 64: 1149.
<https://www.ncbi.nlm.nih.gov/pubmed/15596188>
326. Montorsi, F., *et al.* Is there a role for transrectal microwave hyperthermia of the prostate in the treatment of abacterial prostatitis and prostatodynia? *Prostate*, 1993. 22: 139.
<https://www.ncbi.nlm.nih.gov/pubmed/8456052>
327. Zimmermann, R., *et al.* Extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome in males: a randomised, double-blind, placebo-controlled study. *Eur Urol*, 2009. 56: 418.
<https://www.ncbi.nlm.nih.gov/pubmed/>
328. Zeng, X.Y., *et al.* Extracorporeal shock wave treatment for non-inflammatory chronic pelvic pain syndrome: A prospective, randomized and sham-controlled study. *Chin Med J*, 2012. 125: 114.
<https://www.ncbi.nlm.nih.gov/pubmed/22340476>
329. Vahdatpour B., *et al.* Efficacy of extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome: A randomized, controlled trial. *ISRN Urology*, 2013. 972601.
<https://www.ncbi.nlm.nih.gov/pubmed/24000311>
330. Moayednia, A., *et al.* Long-term effect of extracorporeal shock wave therapy on the treatment of chronic pelvic pain syndrome due to non bacterial prostatitis. *J Res Med Sci*, 2014. 19: 293.
<https://www.ncbi.nlm.nih.gov/pubmed/25097599>
331. Lee, S.H., *et al.* Electroacupuncture relieves pain in men with chronic prostatitis/chronic pelvic pain syndrome: three-arm randomized trial. *Urology*, 2009. 73: 1036.
<https://www.ncbi.nlm.nih.gov/pubmed/19394499>
332. Sahin, S., *et al.* Acupuncture relieves symptoms in chronic prostatitis/chronic pelvic pain syndrome: A randomized, sham-controlled trial. *Prostate Cancer and Prostatic Diseases*, 2015. 18: 249.
<https://www.ncbi.nlm.nih.gov/pubmed/25939517>
333. Chang, S.C., *et al.* The efficacy of acupuncture in managing patients with chronic prostatitis/chronic pelvic pain syndrome: A systemic review and meta-analysis. *NeuroUrology & Urodynamics*, 2016. 6: 6.
<https://www.ncbi.nlm.nih.gov/pubmed/26741647>

334. Qin, Z., *et al.* Systematic review of acupuncture for chronic prostatitis/chronic pelvic pain syndrome. *Medicine (United States)*, 2016. 95: e3095.
<https://www.ncbi.nlm.nih.gov/pubmed/26986148>
335. Kabay, S., *et al.* Efficiency of posterior tibial nerve stimulation in category IIIB chronic prostatitis/chronic pelvic pain: a Sham-Controlled Comparative Study. *Urol Int*, 2009. 83: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/19641356>
336. Nnoaham, K.E., *et al.* Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst Rev*, 2008: Cd003222.
<https://www.ncbi.nlm.nih.gov/pubmed/18646088>
337. Nickel, J.C., *et al.* Sexual function is a determinant of poor quality of life for women with treatment refractory interstitial cystitis. *J Urol*, 2007. 177: 1832.
<https://www.ncbi.nlm.nih.gov/pubmed/17437831>
338. Williams, A.C., *et al.* Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev*, 2012. 11: CD007407.
<https://www.ncbi.nlm.nih.gov/pubmed/23152245>
339. Cheong, Y.C., *et al.* Non-surgical interventions for the management of chronic pelvic pain. *Cochrane Database Syst Rev*, 2014. 3: CD008797.
<https://www.ncbi.nlm.nih.gov/pubmed/24595586>
340. Champaneria, R., *et al.* Psychological therapies for chronic pelvic pain: Systematic review of randomized controlled trials. *Acta Obstetrica et Gynecologica Scandinavica*, 2012. 91: 281.
<https://www.ncbi.nlm.nih.gov/pubmed/22050516>
341. Norman, S.A., *et al.* For whom does it work? Moderators of the effects of written emotional disclosure in a randomized trial among women with chronic pelvic pain. *Psychosom Med*, 2004. 66: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/15039501>
342. Farquhar, C.M., *et al.* A randomized controlled trial of medroxyprogesterone acetate and psychotherapy for the treatment of pelvic congestion. *Br J Obstet Gynaecol*, 1989. 96: 1153.
<https://www.ncbi.nlm.nih.gov/pubmed/2531611>
343. Poleshuck, E.L., *et al.* Randomized controlled trial of interpersonal psychotherapy versus enhanced treatment as usual for women with co-occurring depression and pelvic pain. *J Psychosom Res*, 2014. 77: 264.
<https://www.ncbi.nlm.nih.gov/pubmed/25280823>
344. Kanter, G., *et al.* Mindfulness-based stress reduction as a novel treatment for interstitial cystitis/bladder pain syndrome: a randomized controlled trial. *Int Urogyn J*, 2016. 26: 26.
<https://www.ncbi.nlm.nih.gov/pubmed/27116196>
345. Daniels, J.P., *et al.* Chronic pelvic pain in women. *BMJ*, 2010. 341: c4834.
<https://www.ncbi.nlm.nih.gov/pubmed/20923840>
346. Rosenbaum, T.Y. How well is the multidisciplinary model working? *J Sex Med*, 2011. 8: 2957.
<https://www.ncbi.nlm.nih.gov/pubmed/22032406>
347. Macea, D.D., *et al.* The efficacy of Web-based cognitive behavioral interventions for chronic pain: a systematic review and meta-analysis. *J Pain*, 2010. 11: 917.
<https://www.ncbi.nlm.nih.gov/pubmed/20650691>
348. Bordman, R., *et al.* Below the belt: approach to chronic pelvic pain. *Can Fam Physician*, 2006. 52: 1556.
<https://www.ncbi.nlm.nih.gov/pubmed/17279236>
349. Tripp, D.A., *et al.* A feasibility trial of a cognitive-behavioural symptom management program for chronic pelvic pain for men with refractory chronic prostatitis/chronic pelvic pain syndrome. *Can Urol Assoc J*, 2011. 5: 328.
<https://www.ncbi.nlm.nih.gov/pubmed/22031613>
350. Shoskes, D.A., *et al.* Phenotypically directed multimodal therapy for chronic prostatitis/chronic pelvic pain syndrome: a prospective study using UPOINT. *Urology*, 2010. 75: 1249.
<https://www.ncbi.nlm.nih.gov/pubmed/20363491>
351. Cheah, P.Y., *et al.* Terazosin therapy for chronic prostatitis/chronic pelvic pain syndrome: a randomized, placebo controlled trial. *J Urol*, 2003. 169: 592.
<https://www.ncbi.nlm.nih.gov/pubmed/12544314>
352. Gul, O., *et al.* Use of terazosine in patients with chronic pelvic pain syndrome and evaluation by prostatitis symptom score index. *Int Urol Nephrol*, 2001. 32: 433.
<https://www.ncbi.nlm.nih.gov/pubmed/11583367>

353. Mehik, A., *et al.* Alfuzosin treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, double-blind, placebo-controlled, pilot study. *Urology*, 2003. 62: 425. <https://www.ncbi.nlm.nih.gov/pubmed/12946740>
354. Evliyaoglu, Y., *et al.* Lower urinary tract symptoms, pain and quality of life assessment in chronic non-bacterial prostatitis patients treated with alpha-blocking agent doxazosin; versus placebo. *Int Urol Nephrol*, 2002. 34: 351. <https://www.ncbi.nlm.nih.gov/pubmed/12899226>
355. Tugcu, V., *et al.* A placebo-controlled comparison of the efficiency of triple- and monotherapy in category III B chronic pelvic pain syndrome (CPPS). *Eur Urol*, 2007. 51: 1113. <https://www.ncbi.nlm.nih.gov/pubmed/17084960>
356. Chen, Y., *et al.* Effects of a 6-month course of tamsulosin for chronic prostatitis/chronic pelvic pain syndrome: a multicenter, randomized trial. *World J Urol*, 2011. 29: 381. <https://www.ncbi.nlm.nih.gov/pubmed/20336302>
357. Nickel, J.C., *et al.* A randomized placebo-controlled multicentre study to evaluate the safety and efficacy of finasteride for male chronic pelvic pain syndrome (category IIIA chronic nonbacterial prostatitis). *BJU Int*, 2004. 93: 991. <https://www.ncbi.nlm.nih.gov/pubmed/15142149>
358. Nickel, J.C., *et al.* Silodosin for men with chronic prostatitis/chronic pelvic pain syndrome: results of a phase II multicenter, double-blind, placebo controlled study. *J Urol*, 2011. 186: 125. <https://www.ncbi.nlm.nih.gov/pubmed/21571345>
359. Cohen, J.M., *et al.* Therapeutic intervention for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): A systematic review and meta-analysis. *PLoS ONE*, 2012. 7 (8) (no pagination). <https://www.ncbi.nlm.nih.gov/pubmed/22870266>
360. Anothaisintawee, T., *et al.* Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. *JAMA*, 2011. 305: 78. <https://www.ncbi.nlm.nih.gov/pubmed/21205969>
361. Nickel, J.C., *et al.* Alfuzosin and symptoms of chronic prostatitis-chronic pelvic pain syndrome. *N Engl J Med*, 2008. 359: 2663. <https://www.ncbi.nlm.nih.gov/pubmed/19092152>
362. Nickel, J.C., *et al.* Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial. *J Urol*, 2001. 165: 1539. <https://www.ncbi.nlm.nih.gov/pubmed/11342913>
363. Lee, J.C., *et al.* Prostate biopsy culture findings of men with chronic pelvic pain syndrome do not differ from those of healthy controls. *J Urol*, 2003. 169: 584. <https://www.ncbi.nlm.nih.gov/pubmed/12544312>
364. Nickel, J.C., *et al.* Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: a randomized placebo-controlled multicenter trial. *Urology*, 2003. 62: 614. <https://www.ncbi.nlm.nih.gov/pubmed/14550427>
365. Zhou, Z., *et al.* Detection of nanobacteria infection in type III prostatitis. *Urology*, 2008. 71: 1091. <https://www.ncbi.nlm.nih.gov/pubmed/18538692>
366. Thakkinstian, A., *et al.* Alpha-blockers, antibiotics and anti-inflammatories have a role in the management of chronic prostatitis/chronic pelvic pain syndrome. *BJU Int*, 2012. 110: 1014. <https://www.ncbi.nlm.nih.gov/pubmed/22471591>
367. Leskinen, M., *et al.* Effects of finasteride in patients with inflammatory chronic pelvic pain syndrome: a double-blind, placebo-controlled, pilot study. *Urology*, 1999. 53: 502. <https://www.ncbi.nlm.nih.gov/pubmed/10096374>
368. Kaplan, S.A., *et al.* A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. *J Urol*, 2004. 171: 284. <https://www.ncbi.nlm.nih.gov/pubmed/14665895>
369. Nickel, J.C., *et al.* Failure of a monotherapy strategy for difficult chronic prostatitis/chronic pelvic pain syndrome. *J Urol*, 2004. 172: 551. <https://www.ncbi.nlm.nih.gov/pubmed/15247727>
370. Nickel, J.C., *et al.* Dutasteride reduces prostatitis symptoms compared with placebo in men enrolled in the REDUCE study. *J Urol*, 2011. 186: 1313. <https://www.ncbi.nlm.nih.gov/pubmed/21849186>
371. Wagenlehner, F.M., *et al.* A pollen extract (Cernilton) in patients with inflammatory chronic prostatitis-chronic pelvic pain syndrome: a multicentre, randomised, prospective, double-blind, placebo-controlled phase 3 study. *Eur Urol*, 2009. 56: 544. <https://www.ncbi.nlm.nih.gov/pubmed/19524353>

372. Cai, T., *et al.* Pollen extract in association with vitamins provides early pain relief in patients affected by chronic prostatitis/chronic pelvic pain syndrome. *Exp Ther Med*, 2014. 8: 1032.
<https://www.ncbi.nlm.nih.gov/pubmed/25187793>
373. Shoskes, D.A., *et al.* Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. *Urology*, 1999. 54: 960.
<https://www.ncbi.nlm.nih.gov/pubmed/10604689>
374. Aboumarzouk, O.M., *et al.* Pregabalin for chronic prostatitis. *Cochrane Database Syst Rev*, 2012. 8: CD009063.
<https://www.ncbi.nlm.nih.gov/pubmed/22895982>
375. Pontari, M.A., *et al.* Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial. *Arch Intern Med*, 2010. 170: 1586.
<https://www.ncbi.nlm.nih.gov/pubmed/20876412>
376. Nickel, J.C., *et al.* Pentosan polysulfate sodium therapy for men with chronic pelvic pain syndrome: a multicenter, randomized, placebo controlled study. *J Urol*, 2005. 173: 1252.
<https://www.ncbi.nlm.nih.gov/pubmed/15758763>
377. Gottsch, H.P., *et al.* A pilot study of botulinum toxin A for male chronic pelvic pain syndrome. *Scand J Urol Nephrol*, 2011. 45: 72.
<https://www.ncbi.nlm.nih.gov/pubmed/21062115>
378. Falahatkar, S., *et al.* Transurethral intraprostatic injection of botulinum neurotoxin type A for the treatment of chronic prostatitis/chronic pelvic pain syndrome: Results of a prospective pilot double-blind and randomized placebo-controlled study. *BJU Int*, 2015. 116: 641.
<https://www.ncbi.nlm.nih.gov/pubmed/25307409>
379. Goldmeier, D., *et al.* Treatment of category III A prostatitis with zafirlukast: a randomized controlled feasibility study. *Int J STD AIDS*, 2005. 16: 196.
<https://www.ncbi.nlm.nih.gov/pubmed/15829018>
380. Nickel, J.C., *et al.* Preliminary assessment of safety and efficacy in proof-of-concept, randomized clinical trial of tanezumab for chronic prostatitis/chronic pelvic pain syndrome. *Urology*, 2012. 80: 1105.
<https://www.ncbi.nlm.nih.gov/pubmed/23010344>
381. McNaughton, C.O., *et al.* Allopurinol for chronic prostatitis. *Cochrane Database Syst Rev*, 2002: CD001041.
<https://www.ncbi.nlm.nih.gov/pubmed/12519549>
382. Ziaee, A.M., *et al.* Effect of allopurinol in chronic nonbacterial prostatitis: a double blind randomized clinical trial. *Int Braz J Urol*, 2006. 32: 181.
<https://www.ncbi.nlm.nih.gov/pubmed/16650295>
383. Theoharides, T.C. Hydroxyzine in the treatment of interstitial cystitis. *Urol Clin North Am*, 1994. 21: 113.
<https://www.ncbi.nlm.nih.gov/pubmed/8284834>
384. Seshadri, P., *et al.* Cimetidine in the treatment of interstitial cystitis. *Urology*, 1994. 44: 614.
<https://www.ncbi.nlm.nih.gov/pubmed/7941209>
385. Sant, G.R., *et al.* A pilot clinical trial of oral pentosan polysulfate and oral hydroxyzine in patients with interstitial cystitis. *J Urol*, 2003. 170: 810.
<https://www.ncbi.nlm.nih.gov/pubmed/12913705>
386. Hanno, P.M., *et al.* Use of amitriptyline in the treatment of interstitial cystitis. *J Urol*, 1989. 141: 846.
<https://www.ncbi.nlm.nih.gov/pubmed/2926877>
387. Kirkemo, A., *et al.* Use of amitriptyline in interstitial cystitis. *J Urol*, 1990. 143 Suppl. [No abstract available].
388. Foster, H.E., Jr., *et al.* Effect of amitriptyline on symptoms in treatment naive patients with interstitial cystitis/painful bladder syndrome. *J Urol*, 2010. 183: 1853.
<https://www.ncbi.nlm.nih.gov/pubmed/20303115>
389. Hwang, P., *et al.* Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis. *Urology*, 1997. 50: 39.
<https://www.ncbi.nlm.nih.gov/pubmed/9218016>
390. Mulholland, S.G., *et al.* Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. *Urology*, 1990. 35: 552.
<https://www.ncbi.nlm.nih.gov/pubmed/1693797>
391. Fritjofsson, A., *et al.* Treatment of ulcer and nonulcer interstitial cystitis with sodium pentosanpolysulfate: a multicenter trial. *J Urol*, 1987. 138: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/2442416>

392. van Ophoven, A., *et al.* Safety and efficacy of concurrent application of oral pentosan polysulfate and subcutaneous low-dose heparin for patients with interstitial cystitis. *Urology*, 2005. 66: 707. <https://www.ncbi.nlm.nih.gov/pubmed/16230121>
393. Nickel, J.C., *et al.* Pentosan polysulfate sodium for treatment of interstitial cystitis/bladder pain syndrome: insights from a randomized, double-blind, placebo controlled study. *J Urol*, 2015. 193: 857. <https://www.ncbi.nlm.nih.gov/pubmed/25245489>
394. Oravisto, K.J., *et al.* Treatment of interstitial cystitis with immunosuppression and chloroquine derivatives. *Eur Urol*, 1976. 2: 82. <https://www.ncbi.nlm.nih.gov/pubmed/971677>
395. Forsell, T., *et al.* Cyclosporine in severe interstitial cystitis. *J Urol*, 1996. 155: 1591. <https://www.ncbi.nlm.nih.gov/pubmed/8627830>
396. Moran, P.A., *et al.* Oral methotrexate in the management of refractory interstitial cystitis. *Aust N Z J Obstet Gynaecol*, 1999. 39: 468. <https://www.ncbi.nlm.nih.gov/pubmed/10687766>
397. Barua, J.M., *et al.* A systematic review and meta-analysis on the efficacy of intravesical therapy for bladder pain syndrome/interstitial cystitis. *Int Urogynecol J*, 2016. 27: 1137. <https://www.ncbi.nlm.nih.gov/pubmed/26590137>
398. Asklin, B., *et al.* Intravesical lidocaine in severe interstitial cystitis. Case report. *Scand J Urol Nephrol*, 1989. 23: 311. <https://www.ncbi.nlm.nih.gov/pubmed/2595329>
399. Giannakopoulos, X., *et al.* Chronic interstitial cystitis. Successful treatment with intravesical idocaine. *Arch Ital Urol Nefrol Androl*, 1992. 64: 337. <https://www.ncbi.nlm.nih.gov/pubmed/1462157>
400. Henry, R., *et al.* Absorption of alkalized intravesical lidocaine in normal and inflamed bladders: a simple method for improving bladder anesthesia. *J Urol*, 2001. 165: 1900. <https://www.ncbi.nlm.nih.gov/pubmed/11371877>
401. Parsons, C.L. Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. *Urology*, 2005. 65: 45. <https://www.ncbi.nlm.nih.gov/pubmed/15667861>
402. Nickel, J.C., *et al.* Intravesical alkalinized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. *BJU Int*, 2009. 103: 910. <https://www.ncbi.nlm.nih.gov/pubmed/19021619>
403. Hung, M.J., *et al.* Changes in sexual function of women with refractory interstitial cystitis/bladder pain syndrome after intravesical therapy with a hyaluronic acid solution. *J Sex Med*, 2014. 11: 2256. <https://www.ncbi.nlm.nih.gov/pubmed/24636240>
404. Madersbacher, H., *et al.* GAG layer replenishment therapy for chronic forms of cystitis with intravesical glycosaminoglycans--a review. *Neurourol Urodyn*, 2013. 32: 9. <https://www.ncbi.nlm.nih.gov/pubmed/22782909>
405. Parsons, C.L., *et al.* Treatment of interstitial cystitis with intravesical heparin. *Br J Urol*, 1994. 73: 504. <https://www.ncbi.nlm.nih.gov/pubmed/8012771>
406. Kuo, H.C. Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. *J Formos Med Assoc*, 2001. 100: 309. <https://www.ncbi.nlm.nih.gov/pubmed/11432309>
407. Baykal, K., *et al.* Intravesical heparin and peripheral neuromodulation on interstitial cystitis. *Urol Int*, 2005. 74: 361. <https://www.ncbi.nlm.nih.gov/pubmed/15897705>
408. Dasgupta, P., *et al.* Cimetidine in painful bladder syndrome: a histopathological study. *BJU Int*, 2001. 88: 183. <https://www.ncbi.nlm.nih.gov/pubmed/11488726>
409. Thilagarajah, R., *et al.* Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int*, 2001. 87: 207. <https://www.ncbi.nlm.nih.gov/pubmed/11167643>
410. Kelly, J.D., *et al.* Clinical response to an oral prostaglandin analogue in patients with interstitial cystitis. *Eur Urol*, 1998. 34: 53. <https://www.ncbi.nlm.nih.gov/pubmed/9676414>
411. Korting, G.E., *et al.* A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. *J Urol*, 1999. 161: 558. <https://www.ncbi.nlm.nih.gov/pubmed/9915448>

412. Smith, S.D., *et al.* Improvement in interstitial cystitis symptom scores during treatment with oral L-arginine. *J Urol*, 1997. 158: 703.
<https://www.ncbi.nlm.nih.gov/pubmed/9258064>
413. Lundberg, J.O., *et al.* Elevated nitric oxide in the urinary bladder in infectious and noninfectious cystitis. *Urology*, 1996. 48: 700.
<https://www.ncbi.nlm.nih.gov/pubmed/9836549>
414. Cartledge, J.J., *et al.* A randomized double-blind placebo-controlled crossover trial of the efficacy of L-arginine in the treatment of interstitial cystitis. *BJU Int*, 2000. 85: 421.
<https://www.ncbi.nlm.nih.gov/pubmed/10691818>
415. Ehren, I., *et al.* Effects of L-arginine treatment on symptoms and bladder nitric oxide levels in patients with interstitial cystitis. *Urology*, 1998. 52: 1026.
<https://www.ncbi.nlm.nih.gov/pubmed/9836549>
416. Barbalias, G.A., *et al.* Interstitial cystitis: bladder training with intravesical oxybutynin. *J Urol*, 2000. 163: 1818.
<https://www.ncbi.nlm.nih.gov/pubmed/10799190>
417. van Ophoven, A., *et al.* The dual serotonin and noradrenaline reuptake inhibitor duloxetine for the treatment of interstitial cystitis: results of an observational study. *J Urol*, 2007. 177: 552.
<https://www.ncbi.nlm.nih.gov/pubmed/17222632>
418. Messing, E.M., *et al.* Complication of Clorpactin WCS90 therapy for interstitial cystitis. *Urology*, 1979. 13: 389.
<https://www.ncbi.nlm.nih.gov/pubmed/219578>
419. Murnaghan, G.F., *et al.* Interstitial cystitis--treatment with Chlorpactin WCS 90. *Br J Urol*, 1970. 42: 744.
<https://www.ncbi.nlm.nih.gov/pubmed/5491939>
420. O'Connor, V.J. Clorpactin WCS-90 in the treatment of interstitial cystitis. *Q Bull Northwest Univ Med Sch*, 1955. 29: 392.
<https://www.ncbi.nlm.nih.gov/pubmed/13273619>
421. von Heyden, B., *et al.* [Intravesical therapy of interstitial cystitis]. *Urologe A*, 2000. 39: 542.
<https://www.ncbi.nlm.nih.gov/pubmed/11138274>
422. Wishard, W.N., Jr., *et al.* Use of clorpactin WCS 90 for relief of symptoms due to interstitial cystitis. *J Urol*, 1957. 77: 420.
<https://www.ncbi.nlm.nih.gov/pubmed/13417272>
423. Hanno, P., Interstitial cystitis and related diseases. In: Walsh PC, Retik AB, Stamey TA, Vaughan ED, eds. *Campbell's Urology*, in *Campbell's Urology*. 1998, WB Saunders Co.: Philadelphia.
424. Warren, J.W., *et al.* Urinary tract infection and inflammation at onset of interstitial cystitis/painful bladder syndrome. *Urology*, 2008. 71: 1085.
<https://www.ncbi.nlm.nih.gov/pubmed/18538691>
425. Messelink, E.J. The pelvic pain centre. *World J Urol*, 2001. 19: 208.
<https://www.ncbi.nlm.nih.gov/pubmed/11469609>
426. Gemzell-Danielsson, K., *et al.* The Effect of Age, Parity and Body Mass Index on the Efficacy, Safety, Placement and User Satisfaction Associated With Two Low-Dose Levonorgestrel Intrauterine Contraceptive Systems: Subgroup Analyses of Data From a Phase III Trial. *PLoS One*, 2015. 10: e0135309.
<https://www.ncbi.nlm.nih.gov/pubmed/26378938>
427. Ortmann, O., *et al.* Gonadotrophin-releasing hormone (GnRH) and GnRH agonists: mechanisms of action. *Reprod Biomed Online*, 2002. 5 Suppl 1: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/12537774>
428. Kamanli, A., *et al.* Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. *Rheumatol Int*, 2005. 25: 604.
<https://www.ncbi.nlm.nih.gov/pubmed/15372199>
429. Ho, K.Y., *et al.* Botulinum toxin A for myofascial trigger point injection: a qualitative systematic review. *Eur J Pain*, 2007. 11: 519.
<https://www.ncbi.nlm.nih.gov/pubmed/17071119>
430. Abbott, J.A., *et al.* Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. *Obstet Gynecol*, 2006. 108: 915.
<https://www.ncbi.nlm.nih.gov/pubmed/17012454>
431. Zermann, D., *et al.* Perisphincteric injection of botulinum toxin type A. A treatment option for patients with chronic prostatic pain? *Eur Urol*, 2000. 38: 393.
<https://www.ncbi.nlm.nih.gov/pubmed/11025376>

432. Jarvis, S.K., *et al.* Pilot study of botulinum toxin type A in the treatment of chronic pelvic pain associated with spasm of the levator ani muscles. *Aust N Z J Obstet Gynaecol*, 2004. 44: 46. <https://www.ncbi.nlm.nih.gov/pubmed/15089868>
433. Rao, S.S., *et al.* Clinical trial: effects of botulinum toxin on Levator ani syndrome--a double-blind, placebo-controlled study. *Aliment Pharmacol Ther*, 2009. 29: 985. <https://www.ncbi.nlm.nih.gov/pubmed/19222415>
434. Eckardt, V.F., *et al.* Treatment of proctalgia fugax with salbutamol inhalation. *Am J Gastroenterol*, 1996. 91: 686. <https://www.ncbi.nlm.nih.gov/pubmed/8677929>
435. Atkin, G.K., *et al.* Patient characteristics and treatment outcome in functional anorectal pain. *Dis Colon Rectum*, 2011. 54: 870. <https://www.ncbi.nlm.nih.gov/pubmed/21654255>
436. Chey Wd., *et al.* Effects of 26 weeks of linaclotide treatment on adequate relief and IBS severity in patients with irritable bowel syndrome with constipation. *Gastroenterology*, 2012. 142. [http://www.gastrojournal.org/article/S0016-5085\(12\)63175-8/abstract](http://www.gastrojournal.org/article/S0016-5085(12)63175-8/abstract)
437. Stones, R.W., *et al.* Interventions for treating chronic pelvic pain in women. *Cochrane Database Syst Rev*, 2000: CD000387. <https://www.ncbi.nlm.nih.gov/pubmed/11034686>
438. Remy, C., *et al.* State of the art of paracetamol in acute pain therapy. *Curr Opin Anaesthesiol*, 2006. 19: 562. <https://www.ncbi.nlm.nih.gov/pubmed/16960492>
439. Moore, R.A., *et al.* Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. *Eur J Pain*, 2015. 19: 1213. <https://www.ncbi.nlm.nih.gov/pubmed/25530283>
440. Marjoribanks, J., *et al.* Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*, 2010: CD001751. <https://www.ncbi.nlm.nih.gov/pubmed/20091521>
441. Allen, C., *et al.* Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst Rev*, 2009: CD004753. <https://www.ncbi.nlm.nih.gov/pubmed/19370608>
442. NICE, NCG 173. Neuropathic pain. The pharmacological management of neuropathic pain in adults in non-specialist settings. 2013. <https://www.ncbi.nlm.nih.gov/pubmed/25577930>
443. Baldessarini, R., *Drugs and the treatment of psychiatric disorders.* In: Goodman and Gilman's the pharmacological basis of therapeutics/eds. 1985, New York.
444. Saarto, T., *et al.* Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*, 2007: CD005454. <https://www.ncbi.nlm.nih.gov/pubmed/17943857>
445. Lunn, M.P., *et al.* Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database Syst Rev*, 2009: CD007115. <https://www.ncbi.nlm.nih.gov/pubmed/19821395>
446. Engel, C.C., Jr., *et al.* A randomized, double-blind crossover trial of sertraline in women with chronic pelvic pain. *J Psychosom Res*, 1998. 44: 203. <https://www.ncbi.nlm.nih.gov/pubmed/9532549>
447. Wiffen, P.J., *et al.* Carbamazepine for acute and chronic pain in adults. *Cochrane Database Syst Rev*, 2011: CD005451. <https://www.ncbi.nlm.nih.gov/pubmed/21249671>
448. Moore, R.A., *et al.* Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*, 2011: CD007938. <https://www.ncbi.nlm.nih.gov/pubmed/21412914>
449. Sator-Katzenschlager, S.M., *et al.* Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. *Wien Klin Wochenschr*, 2005. 117: 761. <https://www.ncbi.nlm.nih.gov/pubmed/16416358>
450. Lewis, S.C., *et al.* Gabapentin for the Management of Chronic Pelvic Pain in Women (GaPP1): A Pilot Randomised Controlled Trial. *PLoS ONE [Electronic Resource]*, 2016. 11. <https://www.ncbi.nlm.nih.gov/pubmed/27070434>
451. Moore, R.A., *et al.* Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*, 2009: CD007076. <https://www.ncbi.nlm.nih.gov/pubmed/19588419>

452. Noble, M., *et al.* Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*, 2010: CD006605.
<https://www.ncbi.nlm.nih.gov/pubmed/20091598>
453. The British Pain Society. Opioids for persistent pain: Good practice. 2010.
https://www.britishpainsociety.org/static/uploads/resources/files/book_opioid_main.pdf
454. The British Pain Society. Pain and problem drug use: Information for patients. 2007.
https://www.britishpainsociety.org/static/uploads/resources/files/book_misuse_patients.pdf
455. The British Pain Society. Opioids for persistent pain: Information for patients. 2010.
<https://www.sheffieldpersistentpain.com/assets/Professional%20PDF's/persistent/British%20Pain%20Society%20opioid%20patient%20advice.pdf>
456. Lee, M., *et al.* A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*, 2011. 14: 145.
<https://www.ncbi.nlm.nih.gov/pubmed/21412369>
457. Nickel, J.C. Opioids for chronic prostatitis and interstitial cystitis: lessons learned from the 11th World Congress on Pain. *Urology*, 2006. 68: 697.
<https://www.ncbi.nlm.nih.gov/pubmed/17070334>
458. Sotgiu, M.L., *et al.* Cooperative N-methyl-D-aspartate (NMDA) receptor antagonism and mu-opioid receptor agonism mediate the methadone inhibition of the spinal neuron pain-related hyperactivity in a rat model of neuropathic pain. *Pharmacol Res*, 2009. 60: 284.
<https://www.ncbi.nlm.nih.gov/pubmed/19717013>
459. Olesen, A.E., *et al.* Different effects of morphine and oxycodone in experimentally evoked hyperalgesia: a human translational study. *Br J Clin Pharmacol*, 2010. 70: 189.
<https://www.ncbi.nlm.nih.gov/pubmed/20653672>
460. Kuo, H.C., *et al.* Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. *BJU Int*, 2009. 104: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/19338543>
461. Pinto, R., *et al.* Trigonal injection of botulinum toxin A in patients with refractory bladder pain syndrome/interstitial cystitis. *Eur Urol*, 2010. 58: 360.
<https://www.ncbi.nlm.nih.gov/pubmed/20227820>
462. Kuo, Y.C., *et al.* Adverse Events of Intravesical Onabotulinum Toxin A Injection between Patients with Overactive Bladder and Interstitial Cystitis-Different Mechanisms of Action of Botox on Bladder Dysfunction? *Toxins*, 2016. 8.
<https://www.ncbi.nlm.nih.gov/pubmed/26999201>
463. Akiyama, Y., *et al.* Botulinum toxin type A injection for refractory interstitial cystitis: A randomized comparative study and predictors of treatment response. *Int J Urol*, 2015. 22: 835.
<https://www.ncbi.nlm.nih.gov/pubmed/26041274>
464. Kuo, H.C., *et al.* Intravesical botulinum toxin-A injections reduce bladder pain of interstitial cystitis/bladder pain syndrome refractory to conventional treatment - A prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial. *Neurourology & Urodynamics*, 2015. 24: 24.
<https://www.ncbi.nlm.nih.gov/pubmed/25914337>
465. Lee, C.L., *et al.* Long-term efficacy and safety of repeated intravesical onabotulinumtoxinA injections plus hydrodistention in the treatment of interstitial cystitis/bladder pain syndrome. *Toxins*, 2015. 7: 4283.
<https://www.ncbi.nlm.nih.gov/pubmed/26506388>
466. Pinto, R., *et al.* Persistent therapeutic effect of repeated injections of onabotulinum toxin A in refractory bladder pain syndrome/interstitial cystitis. *J Urol*, 2013. 189: 548.
<https://www.ncbi.nlm.nih.gov/pubmed/23253961>
467. Hanno, P.M., *et al.* Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. *J Urol*, 2015. 193: 1545.
<https://www.ncbi.nlm.nih.gov/pubmed/25623737>
468. Kerr, W.S., Jr. Interstitial cystitis: treatment by transurethral resection. *J Urol*, 1971. 105: 664.
<https://www.ncbi.nlm.nih.gov/pubmed/4397018>
469. Peeker, R., *et al.* Complete transurethral resection of ulcers in classic interstitial cystitis. *Int Urogynecol J Pelvic Floor Dysfunct*, 2000. 11: 290.
<https://www.ncbi.nlm.nih.gov/pubmed/11052564>
470. Rofeim, O., *et al.* Use of the neodymium: YAG laser for interstitial cystitis: a prospective study. *J Urol*, 2001. 166: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/11435840>

471. Warwick, R.T., *et al.* The functional results of partial, subtotal and total cystoplasty with special reference to uretero-caecocystoplasty, selective sphincterotomy and cystocystoplasty. *Br J Urol*, 1967. 39: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/5336762>
472. Freiha, F.S., *et al.* The surgical treatment of intractable interstitial cystitis. *J Urol*, 1980. 123: 632.
<https://www.ncbi.nlm.nih.gov/pubmed/7420547>
473. Shirley, S.W., *et al.* Experiences with colcystoplasties, cecocystoplasties and ileocystoplasties in urologic surgery: 40 patients. *J Urol*, 1978. 120: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/671623>
474. von Garrelts, B. Interstitial cystitis: thirteen patients treated operatively with intestinal bladder substitutes. *Acta Chir Scand*, 1966. 132: 436.
<https://www.ncbi.nlm.nih.gov/pubmed/5972716>
475. Webster, G.D., *et al.* The management of chronic interstitial cystitis by substitution cystoplasty. *J Urol*, 1989. 141: 287.
<https://www.ncbi.nlm.nih.gov/pubmed/2913346>
476. Nurse, D.E., *et al.* The problems of substitution cystoplasty. *Br J Urol*, 1988. 61: 423.
<https://www.ncbi.nlm.nih.gov/pubmed/3395801>
477. Linn, J.F., *et al.* Treatment of interstitial cystitis: comparison of subtrigonal and supratrigonal cystectomy combined with orthotopic bladder substitution. *J Urol*, 1998. 159: 774.
<https://www.ncbi.nlm.nih.gov/pubmed/9474146>
478. Volkmer, B.G., *et al.* Cystectomy and orthotopic ileal neobladder: the impact on female sexuality. *J Urol*, 2004. 172: 2353.
<https://www.ncbi.nlm.nih.gov/pubmed/15538266>
479. Gershbaum, D., *et al.* Practice trends for the management of interstitial cystitis. *Urology*, 2001. 57: 119.
<https://www.ncbi.nlm.nih.gov/pubmed/11378100>
480. Elzawahri, A., *et al.* Urinary conduit formation using a retubularized bowel from continent urinary diversion or intestinal augmentations: ii. Does it have a role in patients with interstitial cystitis? *J Urol*, 2004. 171: 1559.
<https://www.ncbi.nlm.nih.gov/pubmed/15017220>
481. Shaikh, A., *et al.* Pregnancy after augmentation cystoplasty. *J Pak Med Assoc*, 2006. 56: 465.
<https://www.ncbi.nlm.nih.gov/pubmed/17144396>
482. Zhao, Y., *et al.* Circumcision plus antibiotic, anti-inflammatory, and alpha-blocker therapy for the treatment for chronic prostatitis/chronic pelvic pain syndrome: a prospective, randomized, multicenter trial. *World J Urol*, 2015. 33: 617.
<https://www.ncbi.nlm.nih.gov/pubmed/24980414>
483. Oomen, R.J.A., *et al.* Prospective double-blind preoperative pain clinic screening before microsurgical denervation of the spermatic cord in patients with testicular pain syndrome. *Pain*, 2014. 155: 1720.
<https://www.ncbi.nlm.nih.gov/pubmed/24861586>
484. Menconi, C., *et al.* Persistent anal and pelvic floor pain after PPH and STARR: surgical management of the fixed scar staple line. *Int J Colorectal Dis*, 2016. 31: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/26248794>
485. Yoon, S.M., *et al.* Treatment of female urethral syndrome refractory to antibiotics. *Yonsei Med J*, 2002. 43: 644.
<https://www.ncbi.nlm.nih.gov/pubmed/12402379>
486. Costantini, E., *et al.* Treatment of urethral syndrome: a prospective randomized study with Nd:YAG laser. *Urol Int*, 2006. 76: 134.
<https://www.ncbi.nlm.nih.gov/pubmed/16493214>
487. Cheong, Y.C., *et al.* Should women with chronic pelvic pain have adhesiolysis? *BMC Womens Health*, 2014. 14: 36.
<https://www.ncbi.nlm.nih.gov/pubmed/24595586>
488. Swank, D.J., *et al.* Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. *Lancet*, 2003. 361: 1247.
<https://www.ncbi.nlm.nih.gov/pubmed/12699951>
489. Jarrell, J., *et al.* Women's Pain Experience Predicts Future Surgery for Pain Associated With Endometriosis. *J Obstet Gynaecol Can*, 2007. 29: 988.
<https://www.ncbi.nlm.nih.gov/pubmed/18053384>

490. Jarrell, J., *et al.* Laparoscopy and reported pain among patients with endometriosis. *J Obstet Gynaecol Can*, 2005. 27: 477.
<https://www.ncbi.nlm.nih.gov/pubmed/16100643>
491. Baurant, E., *et al.* [Modern algorithm for treating pudendal neuralgia: 212 cases and 104 decompressions]. *J Gynecol Obstet Biol Reprod (Paris)*, 2003. 32: 705.
<https://www.ncbi.nlm.nih.gov/pubmed/15067894>
492. Possover, M., *et al.* Laparoscopic neurolysis of the sacral plexus and the sciatic nerve for extensive endometriosis of the pelvic wall. *Minim Invasive Neurosurg*, 2007. 50: 33.
<https://www.ncbi.nlm.nih.gov/pubmed/17546541>
493. Robert, R., *et al.* Decompression and transposition of the pudendal nerve in pudendal neuralgia: a randomized controlled trial and long-term evaluation. *Eur Urol*, 2005. 47: 403.
<https://www.ncbi.nlm.nih.gov/pubmed/15716208>
494. Robert, R., *et al.* [Pudendal nerve surgery in the management of chronic pelvic and perineal pain]. *Prog Urol*, 2010. 20: 1084.
<https://www.ncbi.nlm.nih.gov/pubmed/21056388>
495. Robert, R., *et al.* Neurosurgical treatment of perineal neuralgias. *Adv Tech Stand Neurosurg*, 2007. 32: 41.
<https://www.ncbi.nlm.nih.gov/pubmed/17907474>
496. NICE. Technology appraisal guidance 159. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. 2008.
<https://www.nice.org.uk/guidance/ta159>
497. Fariello, J.Y., *et al.* Sacral neuromodulation stimulation for IC/PBS, chronic pelvic pain, and sexual dysfunction. *Int Urogynecol J*, 2010. 21: 1553.
<https://www.ncbi.nlm.nih.gov/pubmed/20972541>
498. Peters, K.M., *et al.* A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. *BJU Int*, 2007. 100: 835.
<https://www.ncbi.nlm.nih.gov/pubmed/17822464>
499. Gajewski, J.B., *et al.* The long-term efficacy of sacral neuromodulation in the management of intractable cases of bladder pain syndrome: 14 years of experience in one centre. *BJU Int*, 2011. 107: 1258.
<https://www.ncbi.nlm.nih.gov/pubmed/20883483>
500. Carmel, M., *et al.* Pudendal nerve neuromodulation with neurophysiology guidance: a potential treatment option for refractory chronic pelvi-perineal pain. *Int Urogynecol J*, 2010. 21: 613.
<https://www.ncbi.nlm.nih.gov/pubmed/20012596>
501. Horowitz, S.H. The diagnostic workup of patients with neuropathic pain. *Med Clin North Am*, 2007. 91: 21.
<https://www.ncbi.nlm.nih.gov/pubmed/17164102>
502. Marcelissen, T., *et al.* Sacral neuromodulation as a treatment for neuropathic clitoral pain after abdominal hysterectomy. *Int Urogynecol J*, 2010. 21: 1305.
<https://www.ncbi.nlm.nih.gov/pubmed/20386879>
503. Mayer, R.D., *et al.* Sacral nerve stimulation: neuromodulation for voiding dysfunction and pain. *Neurotherapeutics*, 2008. 5: 107.
<https://www.ncbi.nlm.nih.gov/pubmed/18164489>
504. Falletto, E., *et al.* Is sacral nerve stimulation an effective treatment for chronic idiopathic anal pain? *Dis Colon Rectum*, 2009. 52: 456.
<https://www.ncbi.nlm.nih.gov/pubmed/19333046>
505. Martellucci, J., *et al.* Sacral nerve modulation in the treatment of chronic pain after pelvic surgery. *Colorectal Dis*, 2012. 14: 502.
<https://www.ncbi.nlm.nih.gov/pubmed/21689334>
506. Gokyildiz, S., *et al.* Effects of percutaneous tibial nerve stimulation therapy on chronic pelvic pain. *Gynecol Obstet Invest*, 2012. 73: 99.
<https://www.ncbi.nlm.nih.gov/pubmed/22269443>
507. Eker, H.E., *et al.* Management of neuropathic pain with methylprednisolone at the site of nerve injury. *Pain Med*, 2012. 13: 443.
<https://www.ncbi.nlm.nih.gov/pubmed/22313580>
508. Rhame, E.E., *et al.* Successful treatment of refractory pudendal neuralgia with pulsed radiofrequency. *Pain Physician*, 2009. 12: 633.
<https://www.ncbi.nlm.nih.gov/pubmed/19461829>

8. CONFLICT OF INTEREST

All members of the EAU Chronic Pelvic Pain Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website <http://www.uroweb.org/guidelines/>. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Renal Transplantation

A. Breda (Chair), J. Olsburgh (Vice-chair), K. Budde,
A. Figueiredo, E. Lledó García, H. Regele
Guidelines Associates: R. Boissier, C. Fraser Taylor, V. Hevia,
R.H. Zakri

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Renal Transplantation Guidelines aim to provide a comprehensive overview of the medical and technical aspects relating to renal transplantation.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Renal Transplantation Guidelines panel consists of an international multidisciplinary group of urological surgeons, a nephrologist and a pathologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: <http://www.uroweb.org/guideline/renal-transplantation/>.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is also available, both in print and in a number of versions for mobile devices. These are abridged versions which may require consultation together with the full text version. All are available through the EAU website: <http://www.uroweb.org/guideline/renal-transplantation/>.

1.4 Publication history

The EAU published the first Renal Transplantation Guidelines in 2003 with updates in 2004 and 2009. This document is a comprehensive update of the 2009 Renal Transplantation Guidelines. Additional chapters will be added in the coming year to address ethical issues surrounding kidney transplantation as well as the issue of prior malignancy in kidney transplantation.

2. METHODS

2.1 Introduction

For the 2017 Renal Transplantation Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Renal Transplantation Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between January 1st 2007 and May 31st 2016. A total of 2,601 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: <http://www.uroweb.org/guideline/renal-transplantation/>.

References used in this text are graded according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [1]. Additional information can be found in the general Methodology section of this print, and online at the EAU website; <http://www.uroweb.org/guideline/>. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review and future goals

This document was subject to independent peer review prior to publication.

The results of ongoing and new systematic reviews will be included in the 2018 update of the Renal Transplantation Guidelines. Ongoing systematic reviews include:

1. What are the effectiveness and harms of using kidneys with small renal tumours from deceased or living donors as a source for renal transplantation [2]?
2. For patients with CKD 4/5 and previous urological cancer who subsequently undergo renal transplantation, do they have a higher risk of tumour recurrence compared with patients who do not undergo transplantation [3]?

3. THE GUIDELINE

3.1 Organ retrieval and transplantation surgery

3.1.1 *Living-donor nephrectomy*

The endoscopic (laparoscopic) approach is the preferred technique for living-donor nephrectomy in established kidney transplant programmes [4]. Nevertheless, open surgery, preferably by a mini-incision approach, can still be considered a valid option, despite increased pain in the post-operative period [5].

Endoscopic living-donor nephrectomy (ELDN) includes:

- Pure or hand-assisted transperitoneal laparoscopy;
- Pure or hand-assisted retroperitoneal approach;
- Laparo-Endoscopic Single Site Surgery (LESS);
- Natural orifice transluminal endoscopic surgery-assisted (NOTES);
- Laparo-Endoscopic Single Site Surgery and robotic-assisted transperitoneal or retroperitoneal approach.

There is strong evidence in support of laparoscopic living-donor nephrectomy (LLDN), including several systematic reviews and meta-analysis, which have compared its safety and efficacy to open donor nephrectomy. Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival. However, measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures [6-8].

Standard LLDN is usually done through 5 and 12 mm ports, but has also been done with 3 or 3.5 mm ports [9]. Laparoscopic living-donor nephrectomy can also be performed with robotic assistance, with equivalent results according to a recent systematic review [10]. However, the numbers are still low and a recent paper found a higher complication rate for this approach [11].

Laparo-endoscopic single site surgery nephrectomy allows the surgeon to work through a single incision (usually the umbilicus) with a multi-entry port. The same or a separate incision is then used for kidney withdrawal. Several retrospective and at least three prospective randomised trials demonstrated equivalent safety and results, with a trend towards less pain and better cosmetic results [12]. However, LESS is considered a more technically demanding procedure when compared with classic LLDN and its role is yet to be defined.

Natural orifice transluminal endoscopic surgery-assisted transvaginal nephrectomy avoids the abdominal incision needed for kidney extraction, aimed at minimising scarring and pain. Initial reports suggest that this approach is safe, however experience with this technique is still highly limited [13].

Right LLDN has been considered more difficult, yielding inferior results. However, according to a recent systematic review and meta-analysis right LLDN can be performed with equivalent safety and efficacy [14].

Laparoscopic living-donor nephrectomy has brought attention to potential failures of different devices such as, endoscopic staplers and locking and non-locking clips, used to secure the renal hilum [14]. There is no scientific evidence that one device is safer than another for securing the renal artery [15-17]. However, the U.S. Food and Drug Administration (FDA) and the manufacturers of locking clips have issued a contraindication against their use in securing the artery during LLDN.

Recommendations	LE	GR
Offer pure or hand-assisted laparoscopic/retroperitoneoscopic surgery as the preferential technique for living-donor nephrectomy.	1a	A
Perform laparo-endoscopic single site surgery, robotic and natural orifice transluminal endoscopic surgery-assisted living-donor nephrectomy in highly specialised centres only.	2a	B
Perform open living-donor nephrectomy in centres where endoscopic techniques are not implemented.	1a	A

3.1.2 *Organ preservation*

3.1.2.1 *Kidney storage solutions and cold storage*

There are two main sources for kidney graft injury: ischaemia (warm and cold) and reperfusion injury. The aims of modern kidney storage solutions include: control of cell-swelling during hypothermic ischaemia; maintenance of intra- and extra-cellular electrolyte gradient during ischaemia; buffering of acidosis; provision of energy reserve; and minimisation of oxidative reperfusion injury. There is no agreement on which of the

mechanisms is most important for post-ischaemic renal graft function [18]. No storage solution seems to combine all mechanisms. Previously, Euro-Collins was widely used, but is no longer recommended.

Presently, University of Wisconsin (UW), and histidine-tryptophan-ketoglutarate (HTK) solution are equally effective and are standard for multi-organ or single kidney harvesting procedures (2). The characteristics of HTK are its low viscosity, low potassium concentration and low cost. University of Wisconsin solution has been the standard static cold preservation solution for the procurement of liver, kidney, pancreas, and intestine [19]. University of Wisconsin, HTK, and Celsior solutions have provided similar allograft outcomes in most clinical trials, however, some differences have become apparent in recent studies and registry reports [20, 21]. Marshall's hypertonic citrate solution (MHCS) is also suitable for use in the preservation of human kidneys before transplantation [22]. In experimental studies of kidney preservation, HTK and UW retained a greater capacity to preserve endothelial structure and pH buffering function during warm ischaemia in comparison to MHCS and Celsior, especially in uncontrolled donors after cardiac death (DCD) [23]. In the absence of a cost-utility analysis, the results of the meta-analysis from the randomised controlled trials (RCTs) comparing UW with Celsior and MHSC in standard cadaver donors indicate that these cold storage solutions are equivalent [24].

For living donors, in whom immediate kidney transplantation is planned, perfusion with crystalloid solution is sufficient. Kidneys coming from DCD, especially those uncontrolled are high-risk marginal organs due to prolonged warm ischaemia periods, and require specific measures in order to diminish the rate of non-function or delayed graft function (DGF). More than 60% of kidney grafts currently come from Expanded Criteria Donors (ECD) (any donor aged > 65 years old, and/or donor aged > 55 years with any of the following: acute renal dysfunction, stroke or arterial hypertension) [25].

Recommendations	LE	GR
Use either University of Wisconsin or histidine tryptophane ketoglutarate preservation solutions for cold storage.	1a	A
Use Celsior or Soltran solution for cold storage if University of Wisconsin or histidine tryptophane ketoglutarate solutions are not available.	1b	B

3.1.2.2 Duration of organ preservation

Cold ischaemia time should be as short as possible. Kidneys from elderly (> 55 years) and marginal donors are more sensitive to ischaemia than young kidneys. Organ preservation relies mainly on hypothermia, which lowers the metabolic rate, conserves stores of adenosine triphosphate (ATP), and prevents formation of oxygen-free radicals during the reperfusion phase. Kidneys from deceased donors should ideally be transplanted within 18 hours. Within this 18 hour window, ischaemia time has no significant influence on graft survival [26].

3.1.2.3 Methods of kidney preservation: static and dynamic preservation

Whichever method is used, cold storage is critical. The use of cold preservation as a therapeutic window to deliver pharmacological or gene therapy treatments could, from an investigational point of view, improve both short- and long-term graft outcomes [27]. Cooling reduces the metabolic rate of biological tissue minimising continuous cellular processes that lead to depletion of ATP and accumulation of metabolic products. Reperfusion with oxygenated blood invokes ischaemia-reperfusion injury. Hypothermic perfusion does not enable normal cellular metabolic function or prevent depletion of energy stores [28]. However, it prevents the deleterious effects of simple cooling, especially in the setting of prolonged warm-ischaemic time in uncontrolled DCD. Hypothermic machine perfusion reduces DGF compared with static cold storage [29].

The increased demand for organs has led to the increased use of "higher risk" kidney grafts. Kidneys from DCD or grafts coming from ECDs are more susceptible to preservation injury and have a higher risk of unfavourable outcomes [30, 31].

Dynamic, instead of static, preservation could allow for organ optimisation, offering a platform for viability assessment, active organ repair and resuscitation. *Ex situ* machine perfusion and *in situ* regional perfusion in the donor are emerging as potential tools to preserve vulnerable grafts. Preclinical findings have driven clinical organ preservation research that investigates dynamic preservation, in various modes (continuous, pre-implantation) and temperatures (hypo-, sub-, or normothermic) [28].

There are several methods of kidney preservation including:

- Initial flushing with cold preservation solution followed by ice storage. However, the limitations of static cold storage (CS) in preserving marginal organs such as ECD kidneys has led to the increased use of dynamic methods.

- Current dynamic preservation strategies entering clinical practice and the different modalities of their use are: hypothermic machine perfusion, hypothermic regional perfusion, normothermic machine perfusion, normothermic regional perfusion, subnormothermic machine perfusion and subnormothermic regional perfusion [28].
- Continuous pulsatile hypothermic machine-perfusion (HMP) seems to be a good preservation method for marginal organs, either initially or after a period of simple CS (shipping of suboptimal kidneys) [32].
- Some evidence shows that hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury. The perfusion solutions used are specific, and are qualitatively different to CS solution [24].
- Nonoxygenated HMP of the kidney at low perfusion pressures (20-30 mmHg) has been shown to reduce DGF [29]. The largest RCT comparing simple CS with HMP of deceased donor kidneys showed an overall reduced risk of DGF and a survival benefit, most pronounced in ECD kidneys [33]. Hypothermic machine-perfusion of kidneys from type III DCD decreased DGF with no impact on graft survival [30].
- Hypothermic machine-perfusion reduces the risk of DGF in standard cadaver donor kidneys regardless of cold ischaemia time [34].
- Increased vascular resistance and high perfusate injury marker concentrations are risk factors for DGF, however, they do not justify discarding the kidney. The flow perfusion value seems to be an indicator of graft viability in uncontrolled DCD, particularly donors with high creatinine level [35]. However, research is required to identify a strong and reliable measure for predicting kidney viability from machine perfusion [24]. Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts [36].
- Oxygenation during HMP appears to be beneficial, improving early kidney graft function [37]. The effect of oxygenated HMP is being investigated in two RCTs initiated by the Consortium on Organ Preservation in Europe (COPE), on type III DCD kidneys and ECD kidneys [28].
- A short period of normothermic machine perfusion (NMP) immediately prior to implantation has been shown to improve kidney graft function, replenish ATP and reduce injury in experimental models [38, 39].
- Active research is being developed on preservation of prolonged warm-ischaemically damaged human kidneys (types I and II DCD) by *in situ* normothermic extracorporeal hemoperfusion with oxygenation and leukocyte depletion before procurement [40]. Oxygen carriage is achieved by using blood depleted of leukocytes. Potential advantages of this preservation technique are reduction in ischaemia-reperfusion injury as well as the possibility of assessing organ viability.
- Currently there are no registered ongoing RCTs on pre-implantation NMP using an oxygenated, sanguineous normothermic perfusion solution. However, kidney function can be evaluated during NMP by assessing macroscopic appearance of blood perfusion, renal blood flow and urine output [41].
- Continuous subnormothermic MP and controlled oxygenated rewarming has demonstrated improved creatinine clearance and preservation of structural integrity compared with continuous oxygenated HMP in a research setting [42].

Recommendations	LE	GR
Use cold and warm ischaemia time as predictors of delayed graft function.	1a	A
Use hypothermic machine-perfusion in type III kidneys from donors after cardiac death, kidneys with prolonged simple cold storage and expanded criteria donor kidneys.	1a	A
Hypothermic machine-perfusion may be used in standard criteria deceased donor kidneys.	2a	B
Use low pressure values in hypothermic machine-perfusion preservation.	2a	B
Hypothermic machine-perfusion must be continuous and controlled by pressure and not flow.	1b	B
Do not discard grafts due to only increased vascular resistance and high perfusate injury marker concentrations during hypothermic machine-perfusion preservation.	1b	B

3.1.3 Donor Kidney biopsies

Donor kidney biopsies can serve different purposes including:

- histological assessment of organ quality prior to transplantation (often referred to as procurement or harvest biopsies);
- histological analysis of focal lesions, especially if there is a suspicion of neoplasia;
- detection of donor derived lesions as reference for subsequent post-transplant biopsies (often referred to as baseline, zero-time or implantation biopsies).

3.1.3.1 Procurement Biopsies

3.1.3.1.1 Background and prognostic value

Procurement biopsies are used for the detection of tissue injury to aid the decision of whether or not a deceased donor kidney is suitable for transplantation. These biopsies are most commonly performed in donors with clinical suspicion of chronic kidney injury (ECDs).

Kidney discard in Europe is rarely based on histology findings, as procurement biopsies are not regularly performed for graft allocation in the Eurotransplant region [43]. However, since biopsy findings are the most frequent cause for discarding donor organs in the United States [44-46], their prognostic value has been analysed in numerous studies. A recently published systematic review of studies on donor kidney biopsies revealed a lack of prospective studies and marked heterogeneity regarding the type of lesions being assessed, their scoring, the definitions of post-transplant outcomes and the statistical methods employed [47]. Therefore, the published evidence suggests that the use of procurement biopsies for deciding on suitability for transplantation of donor kidneys may have some important limitations including the following [43, 47, 48]:

- *There is no consistent association between histological lesions observed in donor kidney biopsies and post-transplant outcomes.*

The concept of procurement biopsies in elderly donors was introduced by a study from Gaber *et al.* in 1995. This study observed significantly worse outcomes in recipients of kidneys with > 20% globally sclerotic glomeruli [49]. However, subsequent studies yielded highly variable results and it cannot be concluded that glomerulosclerosis is independently associated with graft outcomes [47]. A similar variability was also observed for other potentially relevant lesions like arterial injury, interstitial fibrosis and tubular atrophy which did show predictive value in some studies but not in others [47].

- *There is no agreement on prognostically relevant lesions and how they should be scored.*

Specific grading systems for donor kidney biopsies have not yet been developed. Lesion scoring in pre-transplant biopsies is mostly based on the Banff consensus for post-transplant renal allograft pathology, which is supported by the 2007 Banff Conference report [50].

Many attempts have been made to use composite semi-quantitative scoring systems to express the global extent of tissue injury in donor kidney biopsies. These scoring systems are mostly based on simple addition of the Banff scores for individual lesions, most commonly glomerulosclerosis, arteriolar hyalinosis, arterial intimal fibrosis, interstitial fibrosis and tubular atrophy and rarely include clinical parameters like donor age [51], serum creatinine values and donor hypertension [52].

A limited number of histological scoring systems are based on modelling analysis [51-55]. Only the Maryland Aggregate Pathology Index (MAPI) [55] scoring system and the Leuven donor risk score [51], use graft failure as their endpoint and have been independently validated in a second cohort. Other studies used surrogate clinical endpoints like DGF [53] and estimated glomerular filtration rate (eGFR) at three months [54] to calculate histological models. In addition, these models were not validated in independent cohorts. The variation in how the components are weighted to achieve the composite score and the different endpoints used may explain the conflicting conclusions in the literature [43, 47, 48].

- *Due to the time constraints of organ allocation procurement biopsies are mostly read on frozen sections by on-call pathologists, which might affect the diagnostic reliability of reported findings.*

This may have substantial impact on the diagnostic reliability of the procedure since frozen sections are prone to morphological artefacts that can impair the detection and scoring of potentially important lesions such as arteriolar hyalinosis and interstitial fibrosis [56, 57]. There is strong evidence that dedicated renal pathologists should examine formalin-fixed paraffin-embedded (FFPE) core-needle biopsies. Paraffin histology employing special stains is technically superior to frozen sections since morphological details are better preserved on paraffin sections than on frozen sections and potentially confounding artefacts can be avoided. Rapid processing of tissue for paraffin histology is technically feasible but the respective protocols are not universally implemented and are not available on a 24/7 basis in most departments. Another source of variability is the professional experience of the pathologist in charge. Procurement biopsies are commonly read by the on-call general pathologist who frequently has no specific training in renal pathology. A recent study specifically addressing this issue found that the on-call pathologists tended to overestimate chronic injury in biopsies [58].

3.1.3.2 Type and size of biopsy

Many transplant centres obtain wedge biopsies of donor kidneys rather than needle biopsies due to the presumed higher risk of bleeding complications with the latter. Wedge biopsies sample the cortex superficially whereas needle biopsies reach deeper aspects of the cortex. Needle biopsies also allow sampling from different areas of the kidney. Several studies comparing wedge with needle biopsies concluded that needle biopsies perform much better in the evaluation of vascular lesions because interlobular arteries are rarely

sampled in wedge biopsies. Both methods were comparable for glomerular or tubulointerstitial lesions [59-62]. It was also demonstrated that glomerulosclerosis is significantly more pronounced in the subcapsular zone compared with deeper areas of the cortex [63]. The problem of insufficient sampling of arteries and over-representation of (subcapsular) glomerular scars in wedge biopsies, can only be avoided if particular attention is paid to the correct performance of the biopsy, with a minimal depth of 5 mm [64]. The predictive value of glomerulosclerosis increases significantly with higher numbers of glomeruli in the wedge biopsy, with ideally at least 25 glomeruli required for evaluation [61].

For surgeons who are reluctant to take needle biopsies, the use of a skin punch biopsy device might be an attractive alternative. Skin punch biopsies measure 3 mm in diameter. They have a shorter length than needle biopsies therefore avoiding injury to large calibre arteries at the corticomedullary junction whilst still sampling tissue from deeper areas of the cortex [65].

3.1.3.3 Key points and recommendations

- Individual histologic lesions like glomerulosclerosis, arterial luminal narrowing or tubulointerstitial injury observed in donor kidney biopsies have limited prognostic value for long-term allograft survival.
- Composite histological scoring systems provide a more comprehensive measure of overall organ damage. Published scoring systems, however, still lack independent validation and robust thresholds.
- Size of the biopsy is of critical importance for its diagnostic value. An adequate biopsy reaches beyond the immediate subcapsular area (≥ 5 mm) and contains ≥ 25 glomeruli and \geq one artery. Needle biopsies, wedge biopsies or specimens obtained with a skin punch biopsy device will result in equally adequate biopsies if sampling is properly performed. Obtaining adequate biopsies with 18 G needles is difficult and requires multiple cores.

Recommendations	LE	GR
Do not base decisions on the acceptance of a donor organ on histological findings alone, since this might lead to an unnecessary high rate of discarded grafts. Interpret histology in context with clinical parameters of donor and recipient including perfusion parameters where available.	3	B
For frozen sections preferably submit 16 G needle core biopsies, wedge biopsies or skin punch biopsies since adequate work-up of very thin specimens in frozen sections is technically difficult.	4	C
Use paraffin histology for histomorphology as it is superior to frozen sections, however, its diagnostic value has to be balanced against a potential delay of transplantation.	3	B
Procurement biopsies should be read by a renal pathologist or a general pathologist with specific training in kidney pathology.	3	B

3.1.3.4 Implantation biopsies

Implantation biopsies are used to provide baseline information on donor kidney injury for comparison with subsequent post-transplant kidney biopsies. Baseline biopsies can be essential for clear distinction between pre-existing damage and acquired lesions. They are particularly valuable in cases of thrombotic microangiopathy, arteriolar hyalinosis or acute tubular injury. In contrast to procurement biopsies that are obtained at the time of organ harvesting, implantation biopsies are usually taken before implantation in order to cover potential effects of cold ischaemia time. Their diagnostic contribution has not been formally quantified in the literature which might be due to the difficulties of measuring the value of implantation biopsies for improving diagnoses. Despite the lack of formal studies investigating their value it seems very reasonable to perform implantation biopsies in deceased donor kidneys.

3.1.4 Living and deceased donor implantation surgery

3.1.4.1 Anaesthetic and peri-operative aspects

Good communication between nephrologists, anaesthetists and surgeons is required for optimal anaesthetic and peri-operative care of the renal transplant patient. Anaesthetic care of the living kidney donor [66] and renal transplant recipient [67] have been reviewed and recent guidelines from the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) [68] are cross referenced.

3.1.4.2 Immediate pre-op haemodialysis

Routine use of haemodialysis immediately prior to renal transplantation is not indicated [68]. Hyperkalaemia is the most common indication for haemodialysis pre-operatively. The risks of haemodialysis compared with medical therapy must be considered along with the risks of intra-operative fluid overload, electrolyte and acid-base disturbances, particularly where a deceased donor kidney is transplanted with a significant risk of DGF. Pre-operative haemodialysis may initiate a pro-inflammatory state, delay surgery, increase the cold ischaemia time and increase the risk of DGF [69, 70].

Recommendation	LE	GR
Manage fluid and electrolyte imbalance prior to transplant surgery with conservative measures where possible.	2	B

3.1.4.3 Operating on patients taking anti-platelet and anti-coagulation agents

Many patients active on the transplant waiting list have vascular disease and/or a pro-thrombotic condition that should be risk-assessed prior to transplantation. Dual anti-platelet therapy is commonly given to patients with coronary artery stents for six to twelve months; peri-operative management plans for these patients should be discussed with a cardiologist so that the risks of withdrawal of the anti-platelet agent can be fully considered. Options for reversal of anti-coagulation and post-operative anti-coagulation should be discussed with a haematologist prior to patient listing.

Some patients will be active on a transplant waiting list whilst continuing to take anti-platelet and/or anti-coagulation agents. The indication for anti-platelet or anti-coagulation agents should be clearly documented for each individual. Potential increased risk of peri-operative bleeding needs to be weighed against potential harm from arterial or venous thrombosis. In accordance with the American College of Chest Physicians and the European Society of Cardiology guidelines [71, 72], the literature suggests that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications [73], however, the number of patients studied was low. If needed, the effect of anti-platelet agents can be reduced with intra-operative platelet infusions.

Recommendations	LE	GR
Consider continuing anti-platelet therapy in patients on the transplant waiting list.	3	C
Discuss patients who take anti-platelet and anti-coagulation agents prior to transplant surgery with relevant cardiologist/haematologist/nephrologist.	4	C

3.1.4.4 What measures should be taken to prevent venous thrombosis including deep vein thrombosis during and after renal transplant?

Peri-operative administration of short-acting anti-coagulation agents reduces peri-operative risk of venous thrombosis (including in ileo-femoral and renal veins), however, due to associated increased blood loss administration requires knowledge of individual patient risk factors. None of the current major thrombosis prevention guidelines directly address thromboprophylaxis in the renal transplant peri-operative period. A small RCT [74] showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation. Those administered prophylactic anti-coagulation had significantly lower haemoglobin whilst those administered prophylactic unfractionated heparin had prolonged lymph drainage. Based on this study, routine pharmacological prophylaxis is not recommended in low-risk living donor recipients. Mechanical measures to decrease ileo-femoral deep vein thrombosis (DVT) can be used where there is no contraindication due to peripheral vascular disease particularly where there are concerns about bleeding risks with pharmacological prophylaxis.

Recommendation	LE	GR
Post-operative prophylactic unfractionated or low-molecular-weight heparin should not be routinely given to low-risk living donor transplant recipients.	1b	B*

*Downgraded due to low power of the RCT.

3.1.4.5 Is there a role for peri-operative antibiotics in renal transplant?

Prophylactic peri-operative antibiotics are generally used in renal transplant surgery but the optimal antibiotic regimen is not known and increasing antibiotic resistance may hamper their effectiveness in this setting. A multicentre, prospective RCT showed no difference at one month in surgical site, bacterial, fungal or viral infection between those receiving a single dose broad spectrum antibiotic at induction of anaesthesia compared to those receiving antibiotic 12 hourly for 3-5 days [75]. A retrospective comparison of peri-operative intravenous cefazolin prophylaxis compared to no antibiotic showed no difference in infectious complications (surgical site, urinary tract, bacteraemia or central catheter-related infection) in the first month after renal transplantation [76].

Recommendation	LE	GR
Use single-dose, rather than multi-dose, peri-operative prophylactic antibiotics in routine renal transplant recipients.	1b	A

3.1.4.6 *Is there a role for specific fluid regimes during renal transplantation and central venous pressure measurement in kidney transplant recipients?*

Careful peri- and post-operative fluid balance is essential for optimal renal graft function. There is no evidence determining if crystalloids or colloids are better for intravenous fluid management during renal transplant surgery, however colloids may be immunogenic. If normal saline (0.9%) is used, monitoring for metabolic acidosis is recommended in the peri-operative period. A prospective double-blind RCT compared normal saline to lactated Ringer's solution as intra-operative intravenous fluid therapy. Serum creatinine at day three post-surgery did not differ between the two groups. However, Ringer's lactate caused less hyperkalaemia and metabolic acidosis than normal saline. Balanced solutions may be the optimal and safer option for intra-operative intravenous fluid therapy [77].

Central venous pressure (CVP) measurement helps anaesthetists guide fluid management. A small prospective non-blinded RCT compared two normal (0.9%) saline regimens: constant infusion (10-12 mL/kg¹/h⁻¹ from start of surgery until reperfusion) and central venous pressure-based infusion (target CVP appropriate to stage of operation) [78]. Central venous pressure directed infusion produced a more stable haemodynamic profile, better diuresis and early graft function. Directed hydration may decrease DGF rates and CVP measurement may help optimise early graft function.

Recommendations	LE	GR
Optimise pre-, peri- and post-operative hydration to improve renal graft function.	1b	B*
Use balanced crystalloid solutions for intra-operative intravenous fluid therapy.	1b	B*
Use target directed intra-operative hydration to decrease delayed graft function rates and optimise early graft function.	1b	B*

*Downgraded due to low power of the RCT.

3.1.4.7 *Is there a role for dopaminergic drugs, furosemide or mannitol in renal transplantation?*

Low-dose dopamine (LDD) has been used in renal transplantation due to a perceived improvement in urine output and early graft function. Use of LDD in kidney donors is outside of the scope of this section. Conflicting results prevent a consensus statement on routine use of LDD in transplant recipients. A small (n=20) prospective randomised cross-over study in deceased donor renal transplantation suggested significant improvements in urine output and creatinine clearance in the first nine hours post-surgery without adverse events [79]. By contrast, a retrospective comparison of LDD in the first twelve hours post-deceased donor renal transplantation showed no difference in diuresis or kidney function but those administered LDD (n=57) had increased heart rates, longer intensive therapy unit stay and higher six-month mortality than those not treated with LDD (n=48) [80].

Considerable variation exists in the use of diuretics during renal transplant recipient surgery and there is little evidence to suggest any benefit from their use [81]. No evidence on the use of mannitol during renal transplant recipient surgery was found during the panels literature search. Use of mannitol in kidney donors is outside of the scope of this section.

Recommendation	LE	GR
Do not routinely use low-dose dopaminergic agents in the early post-operative period.	2b	C

3.1.5 ***Surgical approaches for first, second, third and further transplants***

Transplant (bench/back-table) preparation is a crucial step in the transplantation process. The kidney must be inspected whilst on a sterile iced slush, removing peri-nephric fat when possible to permit inspection of the quality of the organ and to exclude exophytic renal tumours. Biopsy of the kidney on the back-table may be performed to help in the multi-factorial decision making process regarding the quality and usage of the kidney for both single and/or dual transplantation. Suspicious parenchymal lesions also require biopsy. Techniques for intra-operative kidney biopsy are discussed in section 3.1.3.

The number, quality and integrity of renal vessels and ureter(s) should be established and lymphatics at the renal hilum ligated. The quality of the intima of the donor renal artery should be evaluated. Branches of the

renal artery not going to the kidney or ureter(s) should be tied.

In deceased donor kidney transplantation the quality of the aortic patch should be determined. If severe atheroma of the patch, ostium or distal renal artery is seen then the aortic patch and/or distal renal artery can be removed to provide a better quality donor renal artery for implantation. Back table reconstruction of multiple donor arteries is discussed in section 3.1.5.1.

The length of the renal vein should be evaluated. Renal vein branches should be secured/tied. For a deceased donor right kidney, lengthening the renal vein on the back table may be performed if needed with donor inferior vena cava [82]. Techniques for lengthening a short living donor right renal vein from donor gonadal vein or recipient saphenous vein require pre-operative planning and specific consent (discussed in section 3.1.5.1).

The length, quality and number of the ureter(s) should be established. The peri-pelvic and proximal peri-ureteral tissue in the 'golden triangle' should be preserved.

Recommendation	LE	GR
Inspect the kidney to be implanted on the back table before or at the commencement of transplant surgery.	4	A*

*Upgraded based on panel consensus.

3.1.5.1 Single kidney transplant - living and deceased donors

An extra-peritoneal approach to either iliac fossa should be used as the operative approach in most first or second single kidney transplant (SKT) operations. There is no evidence to prefer placement of a left or right kidney into either iliac fossa [83]. Peri-iliac vessel lymphatics should be ligated to try and prevent post-operative lymphocele. Appropriate segments of iliac artery and vein should be mobilised to facilitate appropriate tension free vascular anastomoses and the final positioning of the transplanted kidney.

Recommendations	LE	GR
Choose either iliac fossa for placement of a first or second single kidney transplant.	2	B
Ligate peri-iliac vessel lymphatics (lymphostasis) to reduce post-operative lymphocele.	3	C

A variety of techniques have been described to help with the anastomosis of a short renal vein. This is most commonly encountered with a right kidney especially from a living donor. To achieve equivalent outcomes with right kidneys appropriate surgical technical manoeuvres may be needed to optimise right kidney implantation.

Data from cohort studies [83, 84] and one registry study [85] suggest equivalent outcomes with either left or right deceased donor kidneys. By contrast, another registry study of 2,450 paired kidneys, donated after cardiac death, observed with right kidneys: more early surgical complications; an increased risk in DGF (Odds Ratio [OD] 1.46); and inferior one year graft survival (OD 1.62) but not at subsequent time points [86]. However, surgical techniques used to compensate for a right kidney, anastomosis time and surgeon experience were not recorded.

Data from at least two large registry studies demonstrate a slightly higher risk of early graft failure using right compared to left kidneys from living donors [85, 87, 88]. However, meta-analysis of data from one RCT and fourteen cohort studies suggested equivalent graft outcomes [89].

Techniques to manage a short renal vein can be addressed in the donor and/or recipient. Ligation of internal iliac vein(s) may be necessary to elevate the iliac vein and avoid tension on the renal vein anastomosis [83]. Transposition of the iliac artery and vein may enhance the position for the venous anastomosis [90]. The right renal vein may be lengthened. With deceased donor kidneys this is usually done with donor inferior vena cava (IVC) [84]. In living donors, lengthening of the renal vein may be achieved with donor gonadal vein retrieved at donor nephrectomy [91] or with recipient saphenous vein [92], although both require specific consent and in general the other aforementioned techniques are preferred.

Recommendation	LE	GR
Assess the length of the donor renal vein and if it is short consider one of a variety of surgical techniques to optimise the venous anastomosis.	3	C

A history suggesting previous iliac or femoral vein thrombosis should initiate pre-operative imaging to establish patency of one iliac vein and the IVC. An intra-operative finding of an unexpected iliac vein and/or vena cava thrombosis may lead to abandonment of implantation. With pre-operative planning, native renal (orthotopic) or superior mesenteric vein or gonadal vein collaterals can be used.

The external or common iliac arteries are equally good for arterial anastomosis. The internal iliac artery is more frequently affected by atherosclerosis than the external or common iliac arteries. End-to-side anastomosis of donor renal artery to recipient external and/or common iliac artery is recommended in general over an end-to-end anastomosis to the internal iliac artery. The only RCT comparing these techniques suggests no difference [93]. However, the study was limited by small numbers and a high (8%) overall renal artery thrombosis rate.

The sites of the vascular anastomosis should be chosen carefully according to the length of the renal artery and vein to avoid kinking of the vessels when the kidney is placed into its final location, usually in the iliac fossa. The site of the arterial anastomosis should avoid atheromatous plaques in the iliac artery to decrease the risk of iliac artery dissection. The intima of the donor and recipient arteries should be checked prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior, to or as part of, the arterial anastomosis.

A Carrel patch is usually maintained on a deceased donor renal artery although it can be removed if there is either severe ostial atheroma/stenosis (with good quality proximal renal artery) or if the length of the renal artery is too long for the appropriate implantation site on the iliac artery (which is more common with the right renal artery).

Multiple renal arteries supplying a deceased donor kidney can be maintained on a Carrel patch (of appropriate length) and implanted as a single anastomosis. In living donor transplantation, multiple renal arteries require a variety of strategies to achieve optimum re-perfusion [83]. Two arteries can be implanted separately or to achieve a single anastomosis: a very small second artery (especially if supplying the upper pole) may be sacrificed; the two arteries may be joined together (as a trouser graft); or the smaller artery can be anastomosed onto the side of the main artery (end-to-side anastomoses). A lower polar artery may be re-vascularised via anastomosis to the inferior epigastric artery [94]. In living donor transplantation where three or more donor arteries exist consideration should be given to alternate kidney donors. In circumstances using a living donor kidney with three or more donor arteries, strategies include a combination of the above techniques or, after appropriate consent, use an explanted (recipient's own) internal iliac artery graft [95] or saphenous vein graft [96].

In cases where an iliac artery prosthetic replacement has previously been carried out because of severe symptomatic iliac atheroma, the renal artery should be implanted into the prosthesis. Administration of systemic heparin should be considered prior to clamping of a vascular prosthesis [97].

A variety of sutures and suturing techniques for the vascular anastomosis are described, but in general practice, a 5/0 and 6/0 non-absorbable mono-filament polypropylene suture(s) are used for the renal vein and renal artery anastomosis. Despite this, there is no evidence to recommend one suturing technique over another to prevent, for example, transplant artery stenosis. Use of an expanded polytetrafluoroethylene (ePTFE) suture compared to standard polypropylene suture may reduce blood loss due to a better needle/thread ratio [98].

In third or further transplants the surgical approach must be planned pre-operatively so that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney [99, 100]. Nephrectomy of an old transplant kidney may be required prior to transplantation or at the time of transplantation [99]. Mobilisation of the common or internal iliac artery, internal iliac vein or IVC may be required. An intraperitoneal approach (via the iliac fossa or midline) may be required [101]. Rarely orthotopic transplantation is needed [99, 102].

Recommendations	LE	GR
Use the external or common iliac arteries for an end-to-side arterial anastomosis to donor renal artery.	2	B
An end-to-end anastomosis to the internal iliac artery is an alternative to external or common iliac arteries.	1b	B*
Check the intima of the donor and recipient arteries prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to/as part of the arterial anastomosis.	4	A**
Pre-operatively plan the surgical approach in third or further transplants, to ensure that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney.	3	B

*Downgraded due to low power of study.

**Upgraded based on panel consensus.

3.1.5.1.1 Emerging surgical technologies

Robot-assisted kidney transplant (RAKT) surgery is being evaluated in prospective non-randomised trials (using IDEAL consortium principles) [103]. Whilst potential advantages may exist (decreased post-operative pain, length of hospital stay, incision length and lymphocele rate), evidence is too premature to recommend RAKT.

3.1.5.2 Dual kidney transplants

Dual kidney transplant (DKT) is performed when the quality of a single deceased donor kidney is thought to be insufficient for appropriate long-term graft function and that the outcome with both kidneys would be better. A variety of surgical techniques have been described to implant the pair of donor kidneys [104]. These include unilateral extra-peritoneal (UEP) or intraperitoneal (UIP) and bilateral extra-peritoneal (BEP) or intraperitoneal (BIP) that can be via a midline [105] or two lateral incisions.

The aim of a unilateral approach is to leave the contralateral iliac fossa intact for future transplantation in the event of graft loss and to reduce cold ischaemia time (CIT) for the second kidney transplant [106]. The unilateral approach may require mobilisation and division of the internal iliac vein to facilitate the two renal veins to iliac vein anastomoses. Modifications of the unilateral technique include single renal artery and vein anastomoses (with bench reconstruction) to further reduce CIT for the second kidney [107-109]. Dual kidney transplant takes longer and has higher blood loss than SKT regardless of the technique used. Data suggest shorter operative time and hospital stay with UEP compared to BEP [110] but other data suggest similar outcomes from all DKT techniques. No RCT exist to recommend one technique for all patients or situations.

En-bloc retrieval is performed when kidneys are retrieved from children weighing < 15 kg. Depending on the size of the donor kidney and size and weight of the adult recipient(s), en-bloc transplantation of the two kidneys may be performed or, if appropriate, the aorta and IVC patch may be divided for SKT [111].

3.1.5.3 Ureteric implantation in normal urinary tract

Ureteric anastomotic techniques described for renal transplant recipients with no underlying urological abnormality include: extra (Lich-Gregoir) or intra (Ledbetter-Politano) vesical uretero-neo-cystotomy and uretero-ureterostomy using native ureter. A meta-analysis [112] of two RCTs and 24 observational studies favoured the extra-vesical Lich-Gregoir technique for reduced overall complications (specifically urine leak, stricture and post-operative haematuria). Fewer urinary tract infections (UTIs) were observed with the extra-vesical approach when compared with the intra-vesical technique in one RCT [113].

The donor ureter should be kept as short as possible with peri-ureteric fat preserved to ensure adequate ureteric blood supply. The location on the bladder to position an extra-vesical anastomosis was shown in one small RCT to be advantageous at the posterior bladder rather than anterior position to facilitate future endoscopic manipulation if needed and reported less hydronephrosis post stent removal [114]. Pyelo- or uretero-ureterostomy to the ipsilateral native ureter has been described as a primary technique in recipients with non-refluxing native ureters [115]. In cases where donor ureter has been damaged at retrieval then pyelo-native-ureterostomy or pyelo-neo-cystotomy can be performed. Mono-filament absorbable sutures should be used for the urinary anastomosis to prevent stone formation around the suture material [116].

Recommendations	LE	GR
Perform Lich-Gregoir extra-vesical ureteric anastomosis technique to minimise urinary tract complications in renal transplant recipients with normal urological anatomy.	1a	A
Pyelo/uretero-ureteral anastomosis is an alternative especially for a very short or poorly vascularised transplant ureter.	2b	B

The transplant ureteric anastomosis can be performed with or without a ureteric stent. If a stent is placed a second procedure is generally required for removal. A Cochrane review [117] concluded that stents are recommended to reduce major urological complications, especially urinary leak. The optimal timing for stent removal has yet to be defined but if left over 30 days is associated with more UTIs [118].

Most commonly, stents are removed with local anaesthetic flexible cystoscopy unless there is a need to combine with another procedure warranting general anaesthetic. Various techniques to reduce the morbidity of a second procedure involve tying the stent to the catheter or percutaneous stents but evidence is not yet available as to whether this is beneficial.

Recommendation	LE	GR
Use transplant ureteric stents prophylactically to prevent major urinary complications.	1a	A

Duplex ureters are not infrequently identified at organ retrieval/kidney benching or during work-up for living donor nephrectomy [119, 120]. Duplex ureters can be anastomosed together and then joined to the bladder as one unit (double pant) or kept as two separate anastomoses. This also applies to the two single ureters in DKT in adults or with *en-bloc* transplantation from paediatric donors. The arguments for two separate ureteric anastomoses to the bladder are that an already tenuous blood supply may be further compromised with added suturing and handling, and if there is an issue with one ureter the other should remain unaffected. The advantages to forming one single (two ureter) anastomosis to the bladder are that only one cystotomy is needed; it may be faster and complications may be reduced. There is a lack of high quality evidence relating to duplex ureters.

Recommendation	LE	GR
Anastomose duplex ureters to the bladder either separately or as a combined single anastomosis.	3	C

3.1.5.4 Transplantation/ureteric implantation in abnormal urogenital tract

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- In patients with an ileal conduit, a kidney transplant may be placed upside down to align the ureter to the conduit and avoid a redundant ureter [121].
- The technique used to implant transplant ureter(s) into an ileal conduit is the same as the method used with native ureter(s) (Bricker; Wallace).
- In bladder augmentation or continent pouches, ureters should be implanted with a tunnel technique or extra-vesically (Lich-Gregoir). The latter is favoured in most patients.
- In patients with a Mitrofanoff catheterisable stoma or continent ileo-caecal pouch with catheterisable stoma, consideration should be given to the positioning of the catheterisable stoma (umbilical or iliac fossa - usually right-side) with clear communication with the transplant surgeons so that the position of any future transplant kidney is not compromised. If an intraperitoneal placement of a future kidney transplant is likely, then placement of a Mitrofanoff exiting in the iliac fossa is preferable at the umbilicus. If a future kidney transplant is likely in the right iliac fossa then placement of a Mitrofanoff exiting at the umbilicus or left iliac fossa may be preferable.

3.1.6 Donor complications

Living-donor nephrectomy, like any other intervention, is potentially associated with complications and mortality. However, the fact that the operation is performed on a healthy individual amplifies the relevance of any complications. Potential complications should be included in the process of informed consent.

Reported surgical mortality is 0.01% to 0.03% with no apparent alteration due to changes in surgical techniques or donor selection in recent years [122, 123]. According to a recent systematic review (190 studies) and meta-analysis (40 studies) on complications in minimally invasive LDN, reporting on a total of 32,308 LDNs, intra-operative complications occur in 2.2% (the most common being bleeding in 1.5% and injury to other organs in 0.8%) and post-operative complications occur in 7% (infectious complications in 2.6% and bleeding in 1%) [122]. Conversion to open surgery was reported in 1.1%, half due to bleeding and half due to injury to other organs. Surgical re-interventions occurred in 0.6%; the majority due to bleeding or to evacuate a haematoma [122]. A low trigger for conversion or re-operation should be observed in order to minimise the risk of serious complications.

A recent review looked for complications in 14,964 LDNs performed in the U.S. from 2008-2012 and found an overall peri-operative complication rate of 16.8%, gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), surgical/anaesthesia-related injuries (2.4%), and "other" complications (6.6%). Among the sample, 2.4% required intensive care and in-hospital mortality was 0.007% [11].

Major Clavien Classification of Surgical Complications grade IV or higher affected 2.5% of donors. Risk factors for Clavien grade IV or higher events included obesity (adjusted odds ratio [aOR] 1.55, $p = 0.0005$), pre-donation haematologic (aOR 2.78, $p = 0.0002$), psychiatric conditions (aOR 1.45, $p = 0.04$) and robotic nephrectomy (aOR 2.07, $p = 0.002$). An annual centre volume > 50 (aOR 0.55, $p < 0.0001$) was associated with lower risk [11].

3.1.6.1 Long-term complications

Long-term complications are mostly related to the single-kidney condition. Renal function in living donors decreases after donation before improving for many years, however, in the long run it shows signs of slight deterioration [124, 125]. There is a steady increase in the incidence of proteinuria and hypertension, yet the incidence of end-stage renal disease (0.4-1.1%) does not differ from the general population [124-127]. Long-

term risk of death is no higher than for an age- and co-morbidity-matched population [123, 126].

Health related quality of life (HRQoL), including mental condition, remains on average better than the general population after donation [126-128]. However, some donors experience significant deterioration in their perceived QoL [128]. While global HRQoL is comparable or superior to population normative data, some factors identifiable around time of donation including longer recovery, financial stressors, younger age, higher body mass index (BMI), lower education, smoking and higher expectations prior to donation, may identify donors more likely to develop poor HRQoL, providing an opportunity for intervention [126-128].

Recommendations	LE	GR
Restrict living donor nephrectomy to specialised, preferably high volume, centres.	1	A
Offer long-term follow-up to all living kidney donors.	2a	A*

* Upgraded based on panel consensus.

3.1.7 Recipient complications

3.1.7.1 General complications

Surgical complications during and after kidney transplantation may expose the recipient to an increased risk of morbidity and mortality. The incidence and management of such complications is therefore of primary importance [112, 118, 129-141]. We herein describe in detail the most common surgical complications in renal transplantation.

3.1.7.2 Haemorrhage

Haematomas are usually a minor complication in renal transplantation. Their incidence is reported to be between 0.2-25% [142, 143]. Small and asymptomatic hematomas do not usually require any intervention. In case of larger haematomas, clinical signs and symptoms due to external pressure with graft dysfunction and/or thrombotic graft vessels complications can be present. These cases may be treated by percutaneous drainage under computed tomography (CT) or ultrasound (US) guidance or may require surgical treatment [142].

3.1.7.3 Arterial thrombosis

Transplant renal artery thrombosis is a rare complication with a prevalence ranging from 0.5-3.5% [144]. Usually, it is a consequence of a technical error during the anastomosis although other causes may be related to both the donor and recipient's artery condition (i.e. atherosclerosis), intimal rupture during kidney harvesting, acute rejection episodes, external compression by haematoma or lymphocele, hypercoagulable state, severe hypotension, and toxicity of immunosuppressive agents (cyclosporine or sirolimus) [145]. The clinical manifestations are acute reduction of urine output and the elevation of renal function tests, often resulting in graft loss [142]. The diagnosis is obtained with eco-colour-doppler [142]. Surgical exploration is usually recommended to evaluate the status of the graft. In the rare event the graft appears salvageable, a thrombectomy must be performed. In this situation, the iliac artery is clamped and an arteriotomy versus a dissection of the vascular anastomosis must be performed in order to remove the clot. The graft can be flushed on site and re-vascularised [142]. Unfortunately, in the majority of the situations, the graft is not perfused and therefore an allograft nephrectomy must be performed [142]. Alternatively, thrombolytic agent administration through a catheter directly into the transplant renal artery can be an efficient treatment [144], after the first ten to fourteen post-transplantation days [142].

Recommendations	LE	GR
Perform ultrasound-colour-doppler in case of suspected graft thrombosis.	2b	B
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	2b	B
If arterial thrombosis is confirmed intra-operatively, perform a surgical thrombectomy in case of a salvageable graft or an allograft nephrectomy in case of a non-viable graft .	2b	B
Do not perform directed injection of thrombolytic agents in the renal artery during the first ten to fourteen post-transplantation days due to the high risk of bleeding.	4	C

3.1.7.4 Venous thrombosis

Transplant renal vein thrombosis is an early complication (prevalence 0.5-4%) and one of the most important causes of graft loss during the first post-operative month [146]. The aetiology includes technical errors and/or difficulties during surgery [142] and the hypercoagulable state of the recipient [147, 148]. Colour-doppler-flow-ultrasonography shows absence of venous flow with an abnormal arterial signal (usually a plateau-like reversed diastolic flow). Furthermore, it is common to see an enlargement of the graft due to venous congestion [149].

Surgical exploration is usually recommended despite the fact that the majority of the cases will result in graft loss. In those cases where the venous thrombosis has not resulted in kidney loss at surgical exploration, a venotomy with surgical thrombectomy after clamping the iliac vein can be performed. Alternatively an explantation and subsequent re-implantation can be considered [142]. Thrombolytic agents can also be used, however their results have not been satisfactory [142, 150].

Recommendations	LE	GR
Perform ultrasound-colour-doppler in case of suspected graft thrombosis.	2b	B
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	2b	B
If venous thrombosis is confirmed intra-operatively, perform a surgical thrombectomy in case of a salvageable graft or an allograft nephrectomy in case of a non-viable graft.	2b	B
Pharmacologic prophylaxis to prevent transplant renal vein thrombosis is not currently recommended.	3	B

3.1.7.5 Transplant renal artery stenosis.

The incidence of transplant renal artery stenosis is 1-25% [151, 152]. Risk factors include small calibre and atherosclerosis of the donor artery, trauma to donor artery at procurement, absence of arterial patch, suturing technique (interrupted versus continuous), and damage to the iliac artery during transplantation [153, 154]. It is more common at the site of the anastomosis [153, 154]. It can be suspected in case of arterial hypertension refractory to medical treatment and/or an increase in serum creatinine without hydronephrosis or urinary infection (30). The diagnosis is performed by US-colour-doppler, showing a peak systolic velocity (PSV) of > 200 cm/s in the graft renal artery [153]. In cases of doubt a magnetic resonance angiogram (MRA) or a CT angiogram (CTA) can be performed [155]. It is important to determine whether the stenosis is haemodynamically significant or not. Usually, a stenosis of over 50% is considered a risk for kidney impairment [156]. In case of mild stenosis (< 50%) and absence of symptoms with no deterioration of the allograft, the management is normally conservative although a strict follow-up with US-colour-doppler and clinical parameters has to be adopted due to the possible risk of graft failure [153]. In cases of clinically significant stenosis and/or > 50% on US-colour-doppler, a confirmatory angiogram should be performed. If confirmed and a decision to treat is taken, treatments include percutaneous transluminal angioplasty/stent or surgical intervention. Interventional radiology is typically the first choice although patients considered unsuitable for radiological angioplasty due to recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty may benefit from surgical treatment [153, 154].

Recommendations	LE	GR
Suspect transplant renal artery stenosis in case of refractory arterial hypertension and/or an increasing in serum creatinine without hydronephrosis/infections.	3	B
Perform ultrasound-colour-doppler to diagnose an arterial stenosis.	2a	B
Consider a magnetic resonance or computed tomography angiogram in case of undetermined results on ultrasound.	2a	B
Percutaneous transluminal angioplasty/stent should be the first-line treatment if feasible.	3	B
Offer surgical treatment in case of recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty.	3	B

3.1.7.6 Arteriovenous fistulae and pseudo-aneurysms after renal biopsy

Percutaneous biopsy may result in arteriovenous (AV) fistulae and/or intrarenal pseudo-aneurysms in 1-18% of cases [157]. The aetiology of the AV fistula is related to the simultaneous injury of adjacent arterial and venous branches. A pseudo-aneurysm occurs when only the arterial branch is damaged. Both conditions are diagnosed with US-colour-doppler [142]. The majority of AV fistulae are asymptomatic, resolving in one to two years spontaneously, whilst approximately 30% of them persist and become symptomatic. Typically, the symptoms are hypertension, haematuria, and graft dysfunction due to shunting between arterial and venous vessels. There is an increased risk of spontaneous rupture in case of enlarging pseudo-aneurysms. For both AV fistulae and pseudo-aneurysm, angiographic selective or super selective embolisation represents the treatment of choice [158]. Partial or radical allograft nephrectomy is currently considered the last option [142].

Recommendations	LE	GR
Perform an ultrasound-colour-doppler if an arteriovenous fistulae or pseudo-aneurysm is suspected.	2a	B
Perform angiographic embolisation as first line treatment in symptomatic cases of arteriovenous fistulae or pseudo-aneurysm.	3	C

3.1.7.7 Lymphocele

Lymphocele is a relatively common (1-26%) complication [159]. There is a significant aetiological association with diabetes, m-TOR inhibitors (i.e Sirolimus) therapy, and acute rejection [160]. For large and symptomatic lymphocele, laparoscopic fenestration is associated with the lowest overall recurrence (8%) and complication (14%) rate compared to open surgery and aspiration therapy [161]. Placement of a percutaneous drain (i.e. Fr Pig-Tail) is an option with a success rate as high as 50% [161]. Percutaneous aspiration can be performed although the recurrence rate can be as high as 95% [161], with an increased risk of local infection (6% - 17%) [161]. Furthermore, sclerosant agents such as ethanol, fibrin sealant, gentamicin, or octreotide reduce the recurrence rate compared to simple aspiration [161, 162].

Recommendations	LE	GR
Perform percutaneous drainage placement as the first treatment option.	2a	A*
Perform laparoscopic fenestration when percutaneous treatments fail.	2a	A*
Simple aspiration and sclerosant agents are not recommended as first-line treatment due to the high risk of recurrence.	3	B

* Upgraded based on panel consensus.

3.1.7.8 Urinary leak

Urinary leakage occurs in 0-9.3% of cases [163]. Anastomotic urine leaks can be ureteral or vesical [164]. Ureteral necrosis and/or suture failure are the most important causes [165, 166]. Non-technical risk factors include recipient age, number of renal arteries, site of arterial anastomosis, occurrence of acute rejection episodes, bladder problems, and immunosuppressive regimen [167]. Urinary leak can be suspected by the urine output and the creatinine level in the drain fluid [165]. In order to decrease the risk of ureteral necrosis, it is important to preserve vascularisation of the distal ureter [165]. Furthermore, the routine use of JJ-stent is recommended [166, 168]. The management of urinary leak depends on the location (renal pelvis, proximal or distal ureter, and bladder), the time of appearance and the volume of the leak. For early and low volume urine leaks the treatment may be conservative (i.e. urethral catheter, percutaneous nephrostomy and JJ-stent) [169]. In case of failure of the conservative management, or massive leak, surgical repair must be undertaken. Ureteral re-implantation directly to the bladder or to the native ureter provide similar results [169, 170].

Recommendations	LE	GR
Initial management of a low volume urine leak should include percutaneous nephrostomy tube and/or JJ-stent placement and bladder catheter.	3	C
Perform surgical repair in cases of high volume leak and/or failure of conservative management.	2b	B

3.1.7.9 Ureteral stenosis

Ureteral stenosis is a common complication in recipients, with an incidence of 0.6-10.5% [171]. Early stenosis (within three months of surgery) is usually caused by surgical technique or compromised ureteral blood supply during surgery. Late stenosis (after > six months) is provoked by infection, fibrosis, progressive vascular disease and/or rejection [165, 172]. Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function. The first approach in the management of stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram [171]. The following treatment options depend mainly on the timing, recoverable kidney function, anatomy of the stricture, patient body habitus/comorbidities, and surgeon preference. Strictures < 3 cm in length may be treated endoscopically either with percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision. In this scenario the success rate approaches 50% [173-175]. In case of a recurrence after a primary endourological approach and/or stricture > 3 cm in length, surgical reconstruction should be performed [172] including ureteral direct re-implantation, pyelo-vesical re-implantation (with or without psoas-hitch and/or Boari Flap) or in cases with a normal native ureter, uretero-ureterostomy [176, 177].

Recommendations	GR	LE
In case of ureteral stricture, place a nephrostomy tube for both kidney decompression and stricture diagnosis via an antegrade pyelogram.	2b	B
Endoscopic management (percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision) should be considered for strictures < 3 cm in length.	3	B
Treat late stricture recurrence and/or stricture > 3 cm in length with surgical reconstruction in appropriate recipients.	2b	B

3.1.7.10 Haematuria

The incidence of haematuria ranges from 1-34% [163]. According to the literature, the Lich-Gregoire technique provides the lowest incidence of haematuria (9). Furthermore, meticulous haemostasis during re-implantation results in minimal bleeding [112, 163, 164]. Bladder irrigation is the first line of treatment. Some cases require cystoscopy with evacuation of clots and/or fulguration of bleeding sites [163].

3.1.7.11 Reflux and acute pyelonephritis

The frequency of vesicoureteral reflux is between 1-86% [163, 178]. Acute graft pyelonephritis occurs in 13% of graft recipients. Patients with lower tract urinary infections and cytomegalovirus (CMV) infection present a higher risk of acute graft pyelonephritis [179]. Endoscopic injection of dextranomer/hyaluronic acid copolymer may be the first approach for treatment of vesicoureteral reflux associated with acute pyelonephritis, with a success rate ranging from 57.9% after the first injection to 78.9% after the second injection [180]. Ureteral re-implantation or pyelo-ureterostomy with the native ureter is a viable second treatment option [176].

Recommendations	LE	GR
An endoscopic approach may be the first option for the treatment of symptomatic reflux.	3	B
In case of recurrence (endoscopic failure), a surgical approach should be adopted.	3	B

3.1.7.12 Kidney stones

Urolithiasis occurs in 0.2-1.7% of recipients [181, 182]. The most frequent causes are hyper filtration, renal tubular acidosis, recurrent UTIs, hypocitraturia, hyperoxaluria, hyperuricemia, excessive alkaline urine, persistent tertiary hyperparathyroidism and ureteral strictures [183, 184]. Another risk factor can be urinary anastomosis, with the lowest stone rate using Lich-Gregoir technique [182]. The most frequent clinical signs are fever, increased serum creatinine level, decreased urine output, and haematuria. Pain is usually not referred to due to impaired innervation. A US examination usually provides the diagnosis although a CT of the kidneys, ureters and bladder may be needed to confirm the location and size of the stone [183]. The management depends on the location and size of the stone, and the presence of obstruction. In case of obstructive stones first-line treatment includes placement of a nephrostomy tube, or in some occasions a JJ-stent [185]. Extracorporeal shock wave lithotripsy (ESWL) is usually considered the first approach for stones < 15 mm with stone-free rate varying between 40 and 80% depending on the location of the stone [185]. Ureteroscopy, including antegrade and retrograde approaches, can be considered for stones < 20 mm, with a success rate of up to 67% [115, 182, 186]. For larger stones (> 20 mm), percutaneous nephrolithotomy (PNL) can be offered with a high overall effective stone-free rate (61). In cases of large impacted stones, uretero-ureteral anastomosis, pyelo-ureteral anastomosis, or uretero-vesical re-implantation may provide excellent results for both stone and ureteral obstruction [182].

Recommendations	LE	GR
Evaluate the causes of urolithiasis in the recipient.	2b	B
Treat ureteral obstruction due to a stone with a percutaneous nephrostomy tube or JJ-stent placement.	2b	B
Extracorporeal shockwave lithotripsy should be considered as the first-line treatment option for stones < 15 mm.	2b	B
Antegrade/retrograde ureteroscopy and percutaneous nephrolithotomy may be considered as first- or second-line treatment options as they provide high stone-free rates.	2b	B

3.1.7.13 Wound infection

Wound infections occur in about 4% of the cases. Risk factors include recipients > 60 years, high BMI, anaemia, hypoalbuminemia, long surgical times (> 200 min) [187]. Bacteria commonly involved are *Enterobacteriaceae*, *Staphylococcus aureus* and *Pseudomonas* [176]. Subcutaneous sutures, pre-dialysis transplantation, sealing or ligation of lymphatic trunks, prophylactic fenestration, reducing corticosteroid load,

and avoiding sirolimus/everolimus therapy can decrease wound complication rates [187].

3.1.7.14 *Incisional hernia*

Incisional hernia occurs in approximately 4% of the open kidney transplantations. Risk factors include age, obesity, diabetes, haematoma, rejection, re-operation through the same transplant incision and use of m-TOR inhibitors. Mesh infection is a risk factor for incisional hernia recurrence [188]. Open and laparoscopic repair approaches are safe and effective [188].

3.1.8 **Matching of donors and recipients**

Histocompatibility antigens show remarkable polymorphism and human leukocyte antigen (HLA) matching is still very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches [189-192]. Human leukocyte antigen incompatibility can result in proliferation and activation of the recipient's CD4+ and CD8+ T-cells with concomitant activation of B-cell allo-antibody production. This may lead to cellular and humoral graft rejection. Matching should concentrate on HLA antigens, which impact outcome. Human leukocyte antigens A, B, C as well as DR must be determined in all potential recipients and donors according to current guidelines and national allocation rules [189-194]. Additional, it is recommended to determine HLA-DQ antigens of donor and recipient. Furthermore, HLA-DP antigen characterisation may be performed, especially for sensitised recipients [189-194].

All patients registered for renal transplantation must have their serum screened for anti-HLA antibodies, which are particularly common after pregnancy, previous transplant, transplant rejection, and blood transfusions [189-194]. Thorough pre-transplant testing for HLA antibodies must be performed according to current recommendations [189-194]. Sera from potential organ recipients should be screened for HLA-specific antibodies every three months or as stipulated by the national and/or international organ exchange organisations [189-194]. In addition, screening for HLA-specific antibodies should be carried out at two and four weeks after every immunising event, e.g. blood transfusion, transplantation, pregnancy, and graft explantation [189-194]. Highly sensitised patients should have prioritised access to special allocation programs [191, 192, 194], such as the acceptable mismatch (AM) programme of Eurotransplant [195]. A careful analysis of HLA antibody specificities must be carried out to avoid unacceptable HLA antigens and to determine acceptable HLA antigens in potential donors, who are expected to give a negative cross-match result. The definition of unacceptable HLA antigens should be implemented according to local allocation rules and international recommendations [189-193, 196]. The information on unacceptable HLA antigens should be highlighted with the patient's details in the database of the national kidney-sharing programme, preventing the unnecessary transport of kidneys to recipients with high antibody sensitivity.

To avoid hyper-acute rejection (HAR), adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation in accordance with national and international recommendations [189-192, 194].

Laboratories which provide HLA-testing, HLA antibody testing and cross-matching for transplant centres must have valid accreditation to ensure accuracy and reliability [189-193]. They must follow the standards of national and international organisations, such as the European Federation for Immunogenetics [194].

Previously, compatibility for ABO blood group antigens and HLA antigens was of critical importance in kidney transplantation. This may change in the future, e.g. in the new U.S. allocation system A2 and A2B donors are transplanted into B recipients [192]. To avoid an increasing imbalance between demand and supply in deceased-donor kidney transplantation in O recipients, ABO identity is demanded by several organ allocation organisations with a few exceptions, e.g. as in zero HLA-A+B+DR-mismatch kidneys [192, 193]. With the introduction of antibody elimination methods, potent immunosuppression and novel agents (e.g. anti B-cell drugs), successful ABO-incompatible living donor transplantations, with good long-term outcomes are possible [197, 198]. However, higher costs and infection rates have been described.

Even the barrier of a positive cross-match due to preformed HLA antibodies is under discussion with newer "desensitisation" techniques available in cases with available living donors [199, 200]. Success rates are lower, antibody-mediated rejections are frequent, but survival may be better compared to waiting list survival on dialysis. While this is a rapidly evolving field, further research is needed to define standard protocols. Until then such "desensitisation" protocols are experimental and patients undergoing "desensitisation" should be treated in specialised centres, where outcomes are documented. Patients should be informed adequately on the risks and limitations and alternative strategies (e.g. acceptable miss-match programmes, cross-over transplantation and donor chains) should be discussed.

Recommendations	LE	GR
Determine the ABO blood group and the human leukocyte antigen A, B, C and DR phenotypes for all candidates awaiting kidney transplantation.	3	A*
Testing of donor and recipient for human leukocyte antigen DQ is recommended and human leukocyte antigen DP testing may be performed for sensitised patients.	3	A*
Perform thorough testing for HLA antibodies before transplantation.	3	A*
Perform adequate cross-match tests to avoid hyper-acute rejection, before each kidney and combined kidney/pancreas transplantation.	3	A*

*Upgraded based on panel consensus.

3.1.9 Immunosuppression after kidney transplantation

The principle underlying successful immunosuppression is ‘the balance of survival’. Practitioners must prescribe a dosage of drug high enough to suppress rejection without endangering the recipient’s health. Increased understanding of immune rejection has led to the development of safe modern immunosuppressives [201, 202], which suppress sensitised lymphocyte activity against a transplant. Immunosuppression is particularly important during the initial post-transplant period when there is a high incidence of early post-transplant rejection.

In later post-operative stages, ‘graft adaptation’ occurs, resulting in the very low rejection rates seen in maintenance patients. Rejection prophylaxis should therefore be reduced over time by steroid tapering and gradual lowering of calcineurin inhibitor (CNI) [201-203].

Non-specific side effects of immunosuppression include a higher risk of malignancy and infection, particularly opportunistic infections [201-203]. All immunosuppressants also have dose-dependent specific side effects. Current immunosuppressive protocols aim to reduce drug-specific side effects using a synergistic regimen. A truly synergistic regimen allows profound dose reductions of immunosuppressive drugs; therefore, reducing side effects whilst still maintaining efficacy due to the synergistic effects of the immunosuppressants.

The currently recommended standard initial immunosuppression regime provides excellent efficacy with good tolerability [201-204]. It is given to most patients and consists of:

- calcineurin inhibitors (preferably tacrolimus, alternatively cyclosporine);
- mycophenolate (MMF or enteric-coated mycophenolate sodium [EC-MPS]);
- steroids (prednisolone or methylprednisolone);
- induction therapy (preferably basiliximab in low and standard risk patients and anti-thymocyte globulin (ATG) in high risk patients).

This multidrug regimen reflects the current standard of care for the majority of transplant recipients worldwide [201-203] and may be modified according to local needs and immunological risk. This standard regimen is likely to change as new immunosuppressive drugs and new treatment regimens are developed [201-203]. In addition, any initial drug regimen will need to be tailored to the individual needs of a patient as suggested by the appearance of side effects, lack of efficacy or protocol-driven requirements.

Recommendation	LE	GR
Perform initial rejection prophylaxis with a combination therapy of a calcineurin inhibitor (preferably tacrolimus), mycophenolate, steroids and an induction agent (either basiliximab or anti-thymocyte globulin).	1	A

3.1.9.1 Calcineurin inhibitors

Both cyclosporine and tacrolimus have significant side effects that are hazardous to the graft and patient [201-207]. Most importantly, both are nephrotoxic, and long-term use is an important cause of chronic allograft dysfunction, eventually leading to graft loss or severe chronic kidney disease in recipients of non-renal organs. Both CNIs are considered to be ‘critical-dose’ drugs, so that any deviations from exposure can lead to severe toxicity or failure of efficacy. Because of the narrow therapeutic window and the potential for drug-to-drug interaction, CNIs should be monitored using trough levels, which provide a reasonable estimate for exposure.

Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival [201-207]. Tacrolimus provided better rejection prophylaxis and were associated with better graft survival, when censored for death in some analyses. Renal function was favourable for tacrolimus-treated patients, but did not reach statistical significance in most analyses. Therefore, both CNIs can be used for the effective prevention of acute rejection, but due to higher efficacy tacrolimus is recommended by current guidelines as first-line CNI [202].

For both CNIs several different formulations are available. Precautions (e.g. close surveillance and determination of drug levels) should be instituted after conversion from one formulation to another [208-212]. In case of specific side effects of a CNI (e.g. hirsutism, alopecia, gingival hyperplasia, diabetes, polyoma nephropathy) conversion to the other CNI can be a successful strategy to reduce side effects [201-203]. Due to differences in the efficacy and safety profile, the choice of CNI should include the individual risks and benefits for each patient.

Despite their side effects, CNIs have been a cornerstone of modern immunosuppressive regimens for more than twenty years as they have resulted in an exemplary improvement in kidney graft survival [201, 202]. Future protocols aim to minimise or even eliminate CNIs [203, 206, 213, 214]. However, until such strategies provide superior outcomes, CNIs remain the standard of care [201, 202, 215]. For severe CNI-related side effects, CNI withdrawal, replacement, or profound reduction may be needed [201, 203, 206, 213, 214]. Special attention should be paid to maintenance patients, who may need less CNIs than previously thought [201, 203, 214].

Recommendations	LE	GR
Use calcineurin inhibitors for rejection prophylaxis as they represent current best practice pending publication of long-term results using newer agents.	1	A
Choose a calcineurin inhibitor having taking in to account the immunological risk, characteristics, concomitant immunosuppression, and socio-economic factors of the recipient.	1	A
Use tacrolimus as first-line calcineurin inhibitor due to its higher efficacy.	1	A
Monitor blood-levels of both cyclosporine and tacrolimus to allow appropriate dose adjustment of calcineurin inhibitors.	3	A*

*Upgraded based on panel consensus.

3.1.9.2 Mycophenolates (MPA)

The mycophenolates, MMF and EC-MPS, are based on mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase (IMPDH) [216-220]. This is the rate-limiting step for the synthesis of guanosine monophosphate in the *de novo* purine pathway. As the function and proliferation of lymphocytes is more dependent on *de novo* purine nucleotide synthesis compared to other cell types, IMPDH inhibitors may provide more specific lymphocyte-targeted immunosuppression. The co-administration of mycophenolate with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections [201, 204, 216-220]. Mycophenolic acid is not nephrotoxic; however, it inhibits bone marrow function and may cause CMV infections and gastrointestinal side effects, particularly diarrhoea [216-220]. There is also a higher incidence of polyoma nephropathy, especially when mycophenolate is combined with tacrolimus [221].

Both MPA formulations are equally effective with an almost identical safety profile [201, 216-220], though some prospective studies suggest a better gastrointestinal side-effect profile for EC-MPS in patients who have suffered from MMF-related gastrointestinal complaints, although firm evidence from prospective randomised studies is lacking [216-220].

Standard doses in combination with cyclosporine are MMF 1 g or EC-MPS 720 mg twice daily, although higher initial doses have been suggested [201, 202, 216-220]. Mycophenolic acid is not formally approved for use with tacrolimus, though this is the most frequently used drug combination in many countries worldwide and recommended by guidelines [202]. Despite its frequent use with tacrolimus, there is insufficient evidence to support the optimal dosage for this combination [201, 216, 218]. Tacrolimus has no influence on MPA exposure and leads to approximately 30% higher MPA exposure compared to cyclosporine. Most transplant centres use the same starting dose as in cyclosporine-treated patients, however dose reductions are frequent, especially because of gastrointestinal side effects. Due to the high incidence of side effects, some centres perform a protocol-driven MPA dose reduction in tacrolimus treated patients [216, 218]. Regular monitoring for polyoma is recommended in patients given MPA combined with tacrolimus [201, 221].

Due to a higher incidence of CMV disease with MPA [220], either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted [201, 222]. Cytomegalovirus prophylaxis with antiviral medications (e.g. valganciclovir) should be used routinely in CMV positive recipients and in CMV negative recipients of CMV positive organ transplants, because prophylaxis has recently been shown to reduce CMV disease, CMV-associated mortality in solid organ transplant recipients, and leads to better long-term graft survival in kidney allograft recipients.

The benefit for MPA drug monitoring is uncertain and currently not recommended for the majority of patients [216, 218, 219, 223].

In maintenance patients, the potency of MPA can be used for successful steroid withdrawal in most patients [224] or for substantial dose reductions of nephrotoxic CNIs, which may lead to better renal function [201-204, 206, 214]. Although there have been several studies of the potential for CNI-free protocols with MPA and steroids, complete CNI avoidance or withdrawal over the first three years has been associated with a substantially increased rejection risk and even worse outcomes in prospective randomised studies [201, 203, 214]. In contrast, CNI withdrawal under MPA and steroids appeared to be safe in long-term maintenance patients beyond five years post-transplant and resulted in improved renal function [201, 203, 206, 214, 225].

Recommendation	LE	GR
Administer mycophenolate as part of the initial immunosuppressive regimen.	1	A

3.1.9.3 Azathioprine

Mycophenolate is now routinely used as a primary therapy in place of azathioprine in most units worldwide. In comparison to azathioprine, MPA reduced rejection rates significantly in prospective randomised trials [201, 202, 204, 216-220]. Although a large, prospective study found that azathioprine may give acceptable results in a low-risk population [226], azathioprine is usually reserved for patients who cannot tolerate MPA [201, 202, 216, 217, 219]. When added to dual therapy with cyclosporine and steroids, a meta-analysis found no significant benefit for azathioprine with respect to major outcome parameters [227].

Recommendation	LE	GR
Azathioprine may be used in a low-risk population as a immunosuppressive drug, especially for those intolerant to mycophenolate formulations.	1	A

3.1.9.4 Steroids

Steroids have a large number of side effects [201-203, 224], especially with long-term use. Most practitioners still consider steroids (either prednisolone or methylprednisolone) to be a fundamental adjunct to primary immunosuppression, even though successful steroid withdrawal has been achieved in the vast majority of patients in many prospective, randomised trials [201, 203, 204, 224]. These trials suggest the risk of steroid withdrawal depends on the use of concomitant immuno-suppressive medication, immunological risk, ethnicity, and time after transplantation. Although the risk of rejection diminishes over time, potential benefits may be less prominent after a prolonged steroid treatment period. [201-204, 224].

Recommendations	LE	GR
Initial steroid therapy should be part of immunosuppression in the peri-operative and early post-transplant period.	1	A
Consider steroid withdrawal in standard immunological risk patients on combination therapy with calcineurin inhibitors and mycophenolic acid after the early post-transplant period.	1	A

3.1.9.5 Inhibitors of the mammalian target of rapamycin

The immunosuppressants, sirolimus and everolimus, inhibit the mammalian target of rapamycin (m-TOR) and suppress lymphocyte proliferation and differentiation [201, 213, 228-230]. They inhibit multiple intracellular pathways and block cytokine signals for T-cell proliferation. Similar effects are seen on B-cells, endothelial cells, fibroblasts, and tumour cells. Inhibitors of m-TOR are as effective as MPA when combined with CNIs in preventing rejection [201, 204, 213, 228-230]. However, m-TOR inhibitors exhibit dose-dependent bone marrow toxicity [201, 213, 228-230]. Other potential side effects include hyperlipidaemia, oedema, development of lymphoceles, wound-healing problems, pneumonitis, proteinuria, and impaired fertility.

To date, no prospective comparative studies have been carried out on the m-TOR inhibitors sirolimus and everolimus. Both m-TOR inhibitors have an almost identical side effect profile and mainly differ in their pharmacokinetic properties [201, 213, 228-231]. Sirolimus has a half-life of about 60 hours, is given once a day and is licensed for prophylaxis of kidney recipients only. Everolimus has a half-life of about 24 hours, is licensed for kidney, liver and heart recipients and is given twice a day. Everolimus is licenced for use with cyclosporine and can be given simultaneously with cyclosporine, while sirolimus should be given four hours after cyclosporine. Sirolimus is also licensed in combination therapy with steroids for cyclosporine withdrawal from combination therapy with cyclosporine.

Therapeutic monitoring of trough levels is recommended because of the narrow therapeutic window and the risk of drug-to-drug interactions [201, 213, 228-231].

When combined with CNIs, antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia should be administered for one year following transplantation, e.g. low-dose cotrimoxazole [201, 228-230]. Most importantly, combination therapy with CNIs aggravates CNI-induced nephrotoxicity, although m-TOR inhibitors themselves are non-nephrotoxic [201]. Several studies suggest less favourable outcomes for this combination, especially if CNIs are maintained at standard dosages [201, 204, 206]. Calcineurin inhibitor dosage should therefore be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy [213, 228-232].

Several studies suggest m-TOR inhibitors cannot replace CNIs in the initial phase after transplantation due to lower efficacy and a less favourable side effect profile, particularly wound healing problems and lymphoceles [201, 203, 204, 213, 228-230, 232]. Other trials suggest that m-TOR inhibitors may replace CNI at later stages, e.g. three months after transplantation, with improvements in renal function [201, 203, 204, 206, 213, 228-230, 232]. However, there is an increased risk of rejection and development of HLA antibodies [201, 203, 213, 233], which may be offset by the benefit of the non-nephrotoxic immunosuppression. To date, limited data on long-term follow-up of m-TOR-treated patients have been reported.

Proteinuria and poor renal function at conversion are associated with inferior outcomes [201, 203, 213, 228-230]. Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.

Due to an anti-proliferative effect and a lower incidence of malignancy in m-TOR inhibitor treated patients, conversion from CNIs to m-TOR inhibitors may be beneficial for patients, who develop malignancy after transplantation, or who are at a high risk for the development of post-transplant malignancy or skin cancer [201, 203, 213, 228-230, 232, 234, 235]. Several studies and case reports have suggested that patients with Kaposi sarcoma under CNI therapy benefit from conversion to an m-TOR inhibitor [235].

In summary, m-TOR inhibitors are not recommended as initial immunosuppressive therapy due to their side effect profile and higher discontinuation rates [202]. However, m-TOR inhibitors are a well-studied alternative treatment option.

Recommendations	LE	GR
The m-TOR inhibitors, sirolimus and everolimus, may be used to effectively prevent rejection.	1	A
Significantly reduce calcineurin inhibitor dosage in a combination regimen with m-TOR inhibitors to prevent aggravated nephrotoxicity.	1	A
Take into consideration impaired wound healing and prophylactic surgical measures when m-TOR inhibitors are used as part of the initial immunosuppressive regimen or when patients treated with m-TOR inhibitors undergo major surgery.	1	A
Conversion to m-TOR inhibitors is not recommended for patients with proteinuria and poor renal function.	1	A
Monitor blood-levels of both sirolimus and everolimus to allow for appropriate dose adjustment	3	A

3.1.9.6 Induction with Interleukin-2 receptor antibodies

Basiliximab, a high-affinity anti-interleukin-2 (IL-2) receptor monoclonal antibody is approved for rejection prophylaxis following organ transplantation [201, 202, 204, 236-238]. Basiliximab is given before transplantation and on day four post-transplant. The drug is safe, and IL-2 receptor antibodies have been shown in RCTs to reduce the prevalence of acute cellular rejection by approximately 40% [201, 202, 204, 236-238]. Meta-analyses [204, 236-238] have confirmed the efficacy, although no positive effect on patient or graft survival could be demonstrated, although large retrospective cohort studies and recent large prospective studies suggest such a benefit [201, 202]. Several large controlled trials support the efficacy and safety of quadruple therapy with tacrolimus, mycophenolate and steroids. Interleukin-2 receptor antibodies may allow early steroid withdrawal [224], although higher rejection rates were described. Most importantly, IL-2 receptor antibodies allow a substantial reduction in CNIs, while maintaining excellent efficacy and renal function [201-204, 236-238]. Therefore, this regimen is proposed as first line immunosuppression in patients with low to normal immunological risk [202].

Recommendation	LE	GR
Use interleukin-2 receptor antibodies for induction in patients with normal immunological risk in order to reduce incidence of acute rejection.	1	A

3.1.9.7 T-cell depleting induction therapy

Prophylactic immunosuppression regimens in many countries, particularly the U.S., use potent T-cell depleting 'induction' treatments [201, 202, 204, 236, 239, 240]. Most frequently, ATG is used for prevention of rejection in immunological high risk patients, as recommended by guidelines [202]. In addition these potent biological agents are used for the treatment of severe, steroid resistant rejection episodes [239].

Use of T-cell depleting antibodies in immunological low-risk patients has not been associated with improved long-term outcomes but with an increased risk of severe opportunistic infections and malignancy, particularly post-transplant lymphoproliferative disease [201, 202, 204, 236, 239, 240]. Graft rejection rates are initially lower with induction treatment, however, some studies suggest an increased rejection rate after cessation of lymphocyte depletion [239]. Some centres use these agents to provide effective rejection prophylaxis while initiating CNIs after recovery of the graft from ischaemic injury, although evidence supporting this hypothesis is lacking [239].

Recommendation	LE	GR
T-cell depleting antibodies may be used for induction therapy in immunologically high risk patients.	1	B

3.1.9.8 Belatacept

Belatacept is a fusion protein, which effectively blocks the CD28 co-stimulatory pathway and thereby prevents T-cell activation [213, 241, 242]. Belatacept is intravenously administered and indicated for use as part of a CNI-free regimen together with basiliximab induction, mycophenolate, and corticosteroids. Long-term data from three randomised studies of *de novo* kidney transplant recipients demonstrated better renal function versus cyclosporine-based immunosuppression, although rates and grades of acute rejection were higher for belatacept in the first year post-transplant [201, 204, 213, 241-244]. In patients receiving a standard deceased or living donor kidney, better graft survival was observed, while similar graft survival rates were found with ECDs. Interestingly, belatacept-treated patients had better preserved histology and developed less donor specific antibodies (DSA) compared to cyclosporine. The long-term safety profile of belatacept treated patients was similar to cyclosporine controls, less belatacept treated patients discontinued due to adverse events. In addition, the option of converting patients (either stable patients or due to CNI or m-TOR associated toxicity) was explored with promising initial results [244, 245]. Specific safety signals include a higher rate of post-transplant lymphoproliferative disorder (PTLD) (especially in Epstein-Barr virus (EBV) negative patients), more herpes infections, and tuberculosis in patients from endemic areas [213, 241, 242]. Belatacept was approved in the U.S. and in Europe for EBV positive patients, but is not yet available in many countries. Additional studies are ongoing to fully explore the value of this compound.

Recommendation	LE	GR
Belatacept may be used for immunosuppressive therapy in immunologically low risk patients, who have a positive Epstein-Barr virus serology.	1	B

3.1.10 Immunological complications

Immunological rejection is a common cause of early and late transplant dysfunction [202, 246-248]. There is great variation in the timing and severity of rejection episodes and how they respond to treatment. Today two main types of immunological reactions are distinguished, T-cell mediated rejections (TCMR) and antibody-mediated rejections (ABMR) [202, 246-248]. Antibody-mediated rejection and TCMR may be diagnosed together, called mixed acute rejection. Antibody-mediated rejection may occur as hyperacute rejection (HAR), acute rejection or chronic rejection. Chronic ABMR is considered as one of the leading causes of late graft loss.

The ultimate standard for the diagnosis of rejection is transplant biopsy [202], because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g. acute tubular necrosis, infection, disease recurrence or CNI nephrotoxicity). Therefore, all rejections should be verified by renal biopsy and biopsies should be classified according to the most recent Banff criteria [249], which are the basis for prognosis and treatment [202, 246]. Renal transplant biopsy should be conducted preferably under US control, using an automated needle biopsy system (e.g. tru-cut, biopsy gun) [202] with a 16 G needle

to assure specimen adequacy. The biopsy procedure is considered safe but complications such as bleeding and AV fistulas may occur [202, 250, 251]. The reported risk of major complications (including substantial bleeding, macroscopic haematuria with ureteric obstruction, peritonitis or graft loss) is approximately 1%. Most important contraindications are anti-coagulant therapy including anti-platelet agents and uncontrolled hypertension.

Recommendations	LE	GR
Monitor transplant recipients for signs of acute rejection, particularly during the first six months post-transplant.	3	C
Take regular blood samples in addition to regular monitoring of urine output and ultrasound examinations in order to detect graft dysfunction during hospitalisation.	3	B
Immediately rule out other potential causes of graft dysfunction in cases of suspected acute rejection. An ultrasound of the kidney transplant should be performed.	3	B
There must be routine access to ultrasound-guided biopsy of the transplant and sufficient expertise in the hospital pathology department to allow a rapid and clear-cut diagnosis of rejection or other type of allograft dysfunction.	2	B
Perform a renal biopsy, graded according to the most recent Banff criteria, in patients with suspected acute rejection episodes.	2	B
Only if contraindications to renal biopsy are present, can 'blind' steroid bolus therapy be given.	3	B
Steroid treatment for rejection may start before the renal biopsy is performed.	2	B
Test patients who suffer acute rejection as soon as possible for anti-HLA antibodies against the graft.	2	B
In all patients with rejection, the immunosuppressive therapy should be re-assessed including patient adherence to the medication, which is of particular importance in late rejections.	2	B

3.1.10.1 *Hyper-acute rejection*

Hyper-acute rejection is the most dramatic and destructive immunological attack on the graft [189, 202, 246, 247]. It results from circulating, complement-fixing IgG antibodies, specifically reactive against incompatible donor antigen, which engages with and destroys the vascular endothelium within minutes or hours after vascularisation. It occurs in ABO-incompatible grafts due to the presence of high titres of pre-existing iso-antibodies against blood group antigens. In ABO-matched grafts, HAR is mediated by anti-donor HLA IgG antibodies. With the development of the cross-match test before transplantation, HAR has become an extremely uncommon complication [189]. Imaging and histology reveals generalised infarction of the graft, which has to be treated by graft nephrectomy. Therefore, prevention is crucial, either by avoidance of high iso-antibodies against incompatible blood group antigens in case of an ABO-incompatible renal transplant and/or by performing a regular cross-match before transplantation (see section 3.1.8).

Recommendation	LE	GR
Prevent hyper-acute rejection by adequate ABO blood group and HLA matching of donor and recipients.	3	B

3.1.10.2 *Treatment of T-cell mediated acute rejection*

As only a few randomised trials have investigated different treatment options for this clinical problem, therapy is mainly based on empirical experience rather than on clinical evidence [202, 246]. Parenteral methylprednisolone (500 mg to 1 g) should be given intravenously as one pulse per day for three days. Anuria or a steep rise in the serum creatinine may indicate steroid-refractory rejection and the need for another three day course of pulsed methylprednisolone therapy [202, 246]. In addition, baseline immunosuppression should be optimised to ensure adequate drug exposure [202, 246]. In severe rejection, a conversion from cyclosporine to tacrolimus and/or from azathioprine to mycophenolate is recommended [202, 246].

T-cell depleting biological agents, such as ATG may be given in severe steroid-refractory cases [202, 239, 246]. If biological agents are used, other immunological suppression should be adapted and daily T-cell monitoring should be considered to minimise the dose of the biological agent [239]. Before immunosuppression is intensified, especially before the use of T-cell depleting agents, the prognosis of the graft should be critically assessed against the risks of the aggravated immunosuppression. The patient should be counselled adequately.

Recommendations	LE	GR
Use steroid bolus therapy as first line treatment for T-cell mediated rejection in addition to ensuring adequate baseline immunosuppression.	3	B
In severe or steroid-resistant rejection, consider intensified immunosuppression, high-dose steroid treatment, and T-cell depleting agents.	3	B

3.1.10.3 Treatment of antibody mediated rejection

Antibody mediated rejection is treated in a similar way as T-cell mediated rejection [202, 239, 246, 252-255]. Treatment relies on retrospective studies and empirical treatment guidelines. Treatment with a steroid bolus (at least three days of 500 mg/day) and adequate maintenance therapy with mycophenolate and tacrolimus and sufficient tacrolimus trough levels are common in acute ABMR [202, 246, 252-255]. Although T-cell depleting agents such as ATG appear to have limited value they are frequently used during mixed acute rejection [239]. There are controversial data on the utility of the anti-CD20 antibody, rituximab [202, 246, 252-256]. A retrospective series suggests aggravated toxicity, when rituximab is combined with ATG [257]. In order to target the antibody producing plasma cell, several centres have advocated the use of bortezomib, a proteasome inhibitor approved for the treatment of multiple myeloma [258]. So far, no prospective, randomized trials on bortezomib or other novel agents have been published and neither dose, side effects nor efficacy parameters have been evaluated in a larger cohort of patients with acute ABMR with adequate follow-up.

Some centres advocate intravenous immunoglobulin (IVIG) [202, 246, 252-256], which may modulate and/or suppress antibody production. Intravenous immunoglobulin alone seems insufficient for effective treatment and IVIG is used today in a multimodal regimen. Dosages vary widely from 0.2-2.0 g/kg bodyweight, and no comparative studies (e.g. on the dose or optimal concomitant immunosuppression) have been published.

In addition to drug therapy most centres also try to remove antibodies using plasmapheresis or immune-adsorption columns. Retrospective and prospective case series clearly suggest efficacy [202, 246, 252-256], although details of the procedures vary widely.

Treatment recommendations for chronic ABMR lack firm evidence, and treatment appears to be less successful [246, 252, 254]. Treatment relies on the same principles as for acute ABMR [202, 239, 246, 252-255]. Most centres have similar treatment algorithms and perform antibody elimination together with IVIG and eventually add anti-CD20 and/or bortezomib. Unfortunately, prospective trials on efficacy and side effects are lacking.

In summary, several regimens have proven some efficacy in ABMR. However, except for a beneficial effect of early antibody removal, the lack of firm evidence does not permit evidence-based recommendations for treatment,

Recommendations	LE	GR
Treatment of antibody mediated rejection should include antibody elimination.	1	B
In addition, steroid bolus therapy, adequate maintenance immunosuppression with tacrolimus and mycophenolate, and intravenous immunoglobulin treatment may be used in patients with antibody-mediated rejection.	3	B

3.1.11 Follow-up after transplantation

Long-term graft function is of critical importance for the success of a transplant [202, 203]. Therefore, regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen. Complications of immunosuppression occur frequently including specific complications of the different drugs as well as over immunosuppression (namely opportunistic infections and malignancy) [202, 203]. The risk of cancer and cardiac disease is several-fold higher in transplanted patients than in the general population. Cancer is a cause of significant morbidity and mortality in the transplanted population [202, 259, 260]. Cardiovascular disease is the most frequent cause of death in renal allograft recipients [202, 261, 262]. Other important long-term problems are non-adherence, the development of anti-HLA antibodies, recurrence of the original disease and CNi associated nephrotoxicity [202, 203].

3.1.11.1 Chronic allograft dysfunction/interstitial fibrosis and tubular atrophy

Many patients lose their grafts due to chronic allograft dysfunction [202, 203, 263]. Histology will usually reveal a chronic process of interstitial fibrosis and tubular atrophy (IF/TA) [264]. Some patients will have immunological chronic ABMR [265], as discussed in section 3.1.10.3. Interstitial fibrosis and tubular atrophy takes months or years to develop and is heralded by proteinuria and hypertension, with a simultaneous or delayed rise in serum

creatinine level over months [202, 263, 264]. It is likely that IF/TA is more common in patients who have had early attacks of acute rejection or infection. The main differential diagnoses is chronic nephrotoxicity [266], which is common in patients receiving CNIs, and pre-existing and/or aggravated chronic kidney damage from a marginal donor kidney [202, 263, 264].

Diagnosis is by renal biopsy [202, 263]. In patients diagnosed early, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen [201-203, 263, 264]. Conversion to m-TOR inhibitors is an option for patients without significant proteinuria (< 800 mg/day) but moderate renal function [201-203]. Alternatively, successful conversion to a MPA-based regimen has been described, especially in patients beyond the first three years post-transplant [201, 203, 214]. If there is intolerance to m-TOR inhibitors or MPA, conversion to belatacept or an azathioprine-based regimen may be successful, though the higher risk of rejection warrants close surveillance [44, 245]. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA [203, 214].

In patients with proteinuria, intervention with an angiotensin converting enzyme inhibitor, or angiotensin II receptor blocker [202, 263] together with tight blood pressure control may slow down renal progression. Other supportive measures include the treatment of hypertension, hyperlipidaemia, diabetes, anaemia, acidosis, and bone disease [202]. However, ultimately, the patient will require another transplant (if fit enough to go on the transplant waiting list) or dialysis therapy.

Recommendations	LE	GR
Provide lifelong regular post-transplant follow-up by an experienced and trained transplant specialist at least every six to twelve months.	4	C
Advise patients on appropriate lifestyle changes, potential complications, and the importance of adherence to their immunosuppressive regimen.	4	C
Annual screening should include a dermatological examination, cardiovascular history and exam, tumour screening (including a nodal examination, faecal occult screening, chest X-ray, gynaecological and urological examination), and an abdominal ultrasound, including ultrasound of the native and transplanted kidney. If appropriate further diagnostic tests should be prompted to treat or slow down the progression of any identified complication.	4	C
Regularly monitor (approximately every four to eight weeks) serum creatinine, estimated glomerular filtration rate, blood pressure, urinary protein excretion, immunosuppression and complications after renal transplantation.	4	C
Perform an ultrasound of the graft, in case of graft dysfunction, to rule out obstruction and renal artery stenosis.	4	C
Changes in renal function, blood pressure and urinary protein excretion over time should trigger further diagnostic work-up including renal biopsy, a search for infectious causes and anti-HLA antibodies.	4	C
In patients with interstitial fibrosis and tubular atrophy undergoing calcineurin inhibitor therapy and/or with histological signs suggestive for calcineurin inhibitor toxicity (e.g. arteriolar hyalinosis, striped fibrosis) consider calcineurin inhibitor reduction or withdrawal.	1	A
Initiate appropriate medical treatment, e.g. tight control of hypertension, diabetes, proteinuria, cardiac risk factors, infections, and other complications according to current guidelines.	4	C
Supportive measures should aim to adequately treat the consequences of chronic kidney disease (e.g. anaemia, acidosis, bone disease).	4	C

4. REFERENCES

1. Phillips B, *et al.* Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
2. Bruins, M., *et al.* What are the effectiveness and harms of using kidneys with small renal tumors from deceased or living donors as a source for renal transplantation? PROSPERO, 2016. CRD42016042650.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016042650

3. Bruins, M., *et al.* The risk of tumour recurrence in patients with a history of a urological malignancy who undergo renal transplantation for end-stage renal disease: a systematic review. PROSPERO, 2016. CRD42016046867.
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016046867
4. Lennerling, A., *et al.* Living organ donation practices in Europe - results from an online survey. *Transpl Int*, 2013. 26: 145.
<https://www.ncbi.nlm.nih.gov/pubmed/23198985>
5. Antcliffe, D., *et al.* A meta-analysis of mini-open versus standard open and laparoscopic living donor nephrectomy. *Transpl Int*, 2009. 22: 463.
<https://www.ncbi.nlm.nih.gov/pubmed/19175543>
6. Greco, F., *et al.* Laparoscopic living-donor nephrectomy: analysis of the existing literature. *Eur Urol*, 2010. 58: 498.
<https://www.ncbi.nlm.nih.gov/pubmed/20417024>
7. Wilson, C.H., *et al.* Laparoscopic versus open nephrectomy for live kidney donors. *Cochrane Database Syst Rev*, 2011: CD006124.
<https://www.ncbi.nlm.nih.gov/pubmed/22071829>
8. Yuan, H., *et al.* The safety and efficacy of laparoscopic donor nephrectomy for renal transplantation: an updated meta-analysis. *Transplant Proc*, 2013. 45: 65.
<https://www.ncbi.nlm.nih.gov/pubmed/23375276>
9. Breda, A., *et al.* Mini-laparoscopic live donor nephrectomy with the use of 3-mm instruments and laparoscope. *World J Urol*, 2015. 33: 707.
<https://www.ncbi.nlm.nih.gov/pubmed/25182807>
10. Giacomoni, A., *et al.* Robotic nephrectomy for living donation: surgical technique and literature systematic review. *Am J Surg*, 2016. 211: 1135.
<https://www.ncbi.nlm.nih.gov/pubmed/26499052>
11. Lentine, K.L., *et al.* Perioperative Complications After Living Kidney Donation: A National Study. *Am J Transplant*, 2016. 16: 1848.
<https://www.ncbi.nlm.nih.gov/pubmed/26700551>
12. Autorino, R., *et al.* Laparoendoscopic single-site (LESS) vs laparoscopic living-donor nephrectomy: a systematic review and meta-analysis. *BJU Int*, 2015. 115: 206.
<https://www.ncbi.nlm.nih.gov/pubmed/24588876>
13. Alcaraz, A., *et al.* Feasibility of transvaginal natural orifice transluminal endoscopic surgery-assisted living donor nephrectomy: is kidney vaginal delivery the approach of the future? *Eur Urol*, 2011. 59: 1019.
<https://www.ncbi.nlm.nih.gov/pubmed/21458151>
14. Liu, N., *et al.* Maximizing the donor pool: left versus right laparoscopic live donor nephrectomy--systematic review and meta-analysis. *Int Urol Nephrol*, 2014. 46: 1511.
<https://www.ncbi.nlm.nih.gov/pubmed/24595603>
15. Hsi, R.S., *et al.* Analysis of techniques to secure the renal hilum during laparoscopic donor nephrectomy: review of the FDA database. *Urology*, 2009. 74: 142.
<https://www.ncbi.nlm.nih.gov/pubmed/19406458>
16. Hsi, R.S., *et al.* Mechanisms of hemostatic failure during laparoscopic nephrectomy: review of Food and Drug Administration database. *Urology*, 2007. 70: 888.
<https://www.ncbi.nlm.nih.gov/pubmed/17919695>
17. Ponsky, L., *et al.* The Hem-o-lok clip is safe for laparoscopic nephrectomy: a multi-institutional review. *Urology*, 2008. 71: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/18295866>
18. Irish, W.D., *et al.* A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. *Am J Transplant*, 2010. 10: 2279.
<https://www.ncbi.nlm.nih.gov/pubmed/20883559>
19. de Boer, J., *et al.* Eurotransplant randomized multicenter kidney graft preservation study comparing HTK with UW and Euro-Collins. *Transpl Int*, 1999. 12: 447.
<https://www.ncbi.nlm.nih.gov/pubmed/10654357>
20. Parsons, R.F., *et al.* Preservation solutions for static cold storage of abdominal allografts: which is best? *Curr Opin Organ Transplant*, 2014. 19: 100.
<https://www.ncbi.nlm.nih.gov/pubmed/24553501>
21. Tillou, X., *et al.* Comparison of UW and Celsior: long-term results in kidney transplantation. *Ann Transplant*, 2013. 18: 146.
<https://www.ncbi.nlm.nih.gov/pubmed/23792514>

22. Barnett, D., *et al.* Machine perfusion systems and cold static storage of kidneys from deceased donors. NICE Guidelines. Technology appraisal guidance 2009.
<https://www.nice.org.uk/guidance/ta165>
23. Kay, M.D., *et al.* Comparison of preservation solutions in an experimental model of organ cooling in kidney transplantation. *Br J Surg*, 2009. 96: 1215.
<https://www.ncbi.nlm.nih.gov/pubmed/19787767>
24. Bond, M., *et al.* The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model. *Health Technol Assess*, 2009. 13: iii.
<https://www.ncbi.nlm.nih.gov/pubmed/19674537>
25. Lledo-Garcia, E., *et al.* Spanish consensus document for acceptance and rejection of kidneys from expanded criteria donors. *Clin Transplant*, 2014. 28: 1155.
<https://www.ncbi.nlm.nih.gov/pubmed/25109314>
26. Opelz, G., *et al.* Multicenter analysis of kidney preservation. *Transplantation*, 2007. 83: 247.
<https://www.ncbi.nlm.nih.gov/pubmed/17297393>
27. Chatauret, N., *et al.* Preservation strategies to reduce ischemic injury in kidney transplantation: pharmacological and genetic approaches. *Curr Opin Organ Transplant*, 2011. 16: 180.
<https://www.ncbi.nlm.nih.gov/pubmed/21415820>
28. Jochmans, I., *et al.* Past, Present, and Future of Dynamic Kidney and Liver Preservation and Resuscitation. *Am J Transplant*, 2016. 16: 2545.
<https://www.ncbi.nlm.nih.gov/pubmed/26946212>
29. O'Callaghan, J.M., *et al.* Systematic review and meta-analysis of hypothermic machine perfusion versus static cold storage of kidney allografts on transplant outcomes. *Br J Surg*, 2013. 100: 991.
<https://www.ncbi.nlm.nih.gov/pubmed/23754643>
30. Jochmans, I., *et al.* Machine perfusion versus cold storage for the preservation of kidneys donated after cardiac death: a multicenter, randomized, controlled trial. *Ann Surg*, 2010. 252: 756.
<https://www.ncbi.nlm.nih.gov/pubmed/21332580>
31. Reznik, O.N., *et al.* Machine perfusion as a tool to select kidneys recovered from uncontrolled donors after cardiac death. *Transplant Proc*, 2008. 40: 1023.
<https://www.ncbi.nlm.nih.gov/pubmed/18555105>
32. Jochmans, I., *et al.* Hypothermic machine perfusion of kidneys retrieved from standard and high-risk donors. *Transpl Int*, 2015. 28: 665.
<https://www.ncbi.nlm.nih.gov/pubmed/25630347>
33. Treckmann, J., *et al.* Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death. *Transpl Int*, 2011. 24: 548.
<https://www.ncbi.nlm.nih.gov/pubmed/21332580>
34. Gill, J., *et al.* Pulsatile perfusion reduces the risk of delayed graft function in deceased donor kidney transplants, irrespective of donor type and cold ischemic time. *Transplantation*, 2014. 97: 668.
<https://www.ncbi.nlm.nih.gov/pubmed/24637865>
35. Matsuno, N., *et al.* Machine perfusion preservation for kidney grafts with a high creatinine from uncontrolled donation after cardiac death. *Transplant Proc*, 2010. 42: 155.
<https://www.ncbi.nlm.nih.gov/pubmed/20172304>
36. Jochmans, I., *et al.* Graft quality assessment in kidney transplantation: not an exact science yet! *Curr Opin Organ Transplant*, 2011. 16: 174.
<https://www.ncbi.nlm.nih.gov/pubmed/21383549>
37. Thuillier, R., *et al.* Benefits of active oxygenation during hypothermic machine perfusion of kidneys in a preclinical model of deceased after cardiac death donors. *J Surg Res*, 2013. 184: 1174.
<https://www.ncbi.nlm.nih.gov/pubmed/23731682>
38. Hosgood, S.A., *et al.* Normothermic machine perfusion of the kidney: better conditioning and repair? *Transpl Int*, 2015. 28: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/24629095>
39. Reddy, S.P., *et al.* Normothermic perfusion: a mini-review. *Transplantation*, 2009. 87: 631.
<https://www.ncbi.nlm.nih.gov/pubmed/19295304>
40. Reznik, O., *et al.* Kidney from uncontrolled donors after cardiac death with one hour warm ischemic time: resuscitation by extracorporeal normothermic abdominal perfusion "in situ" by leukocytes-free oxygenated blood. *Clin Transplant*, 2011. 25: 511.
<https://www.ncbi.nlm.nih.gov/pubmed/20973824>
41. Hosgood, S.A., *et al.* Ex vivo normothermic perfusion for quality assessment of marginal donor kidney transplants. *Br J Surg*, 2015. 102: 1433.
<https://www.ncbi.nlm.nih.gov/pubmed/26313559>

42. Hoyer, D.P., *et al.* Subnormothermic machine perfusion for preservation of porcine kidneys in a donation after circulatory death model. *Transpl Int*, 2014. 27: 1097.
<https://www.ncbi.nlm.nih.gov/pubmed/24963744>
43. Naesens, M. Zero-Time Renal Transplant Biopsies: A Comprehensive Review. *Transplantation*, 2016. 100: 1425.
<https://www.ncbi.nlm.nih.gov/pubmed/26599490>
44. Kasiske, B.L., *et al.* The role of procurement biopsies in acceptance decisions for kidneys retrieved for transplant. *Clin J Am Soc Nephrol*, 2014. 9: 562.
<https://www.ncbi.nlm.nih.gov/pubmed/24558053>
45. Marrero, W.J., *et al.* Predictors of Deceased Donor Kidney Discard in the United States. *Transplantation*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27163541>
46. Sung, R.S., *et al.* Determinants of discard of expanded criteria donor kidneys: impact of biopsy and machine perfusion. *Am J Transplant*, 2008. 8: 783.
<https://www.ncbi.nlm.nih.gov/pubmed/18294347>
47. Wang, C.J., *et al.* The Donor Kidney Biopsy and Its Implications in Predicting Graft Outcomes: A Systematic Review. *Am J Transplant*, 2015. 15: 1903.
<https://www.ncbi.nlm.nih.gov/pubmed/25772854>
48. Hopfer, H., *et al.* Assessment of donor biopsies. *Curr Opin Organ Transplant*, 2013. 18: 306.
<https://www.ncbi.nlm.nih.gov/pubmed/23492644>
49. Gaber, L.W., *et al.* Glomerulosclerosis as a determinant of posttransplant function of older donor renal allografts. *Transplantation*, 1995. 60: 334.
<https://www.ncbi.nlm.nih.gov/pubmed/7652761>
50. Solez, K., *et al.* Banff 07 classification of renal allograft pathology: updates and future directions. *Am J Transplant*, 2008. 8: 753.
<https://www.ncbi.nlm.nih.gov/pubmed/18294345>
51. De Vusser, K., *et al.* The predictive value of kidney allograft baseline biopsies for long-term graft survival. *J Am Soc Nephrol*, 2013. 24: 1913.
<https://www.ncbi.nlm.nih.gov/pubmed/23949799>
52. Anglicheau, D., *et al.* A simple clinico-histopathological composite scoring system is highly predictive of graft outcomes in marginal donors. *Am J Transplant*, 2008. 8: 2325.
<https://www.ncbi.nlm.nih.gov/pubmed/18785957>
53. Balaz, P., *et al.* Identification of expanded-criteria donor kidney grafts at lower risk of delayed graft function. *Transplantation*, 2013. 96: 633.
<https://www.ncbi.nlm.nih.gov/pubmed/23912171>
54. Lopes, J.A., *et al.* Evaluation of pre-implantation kidney biopsies: comparison of Banff criteria to a morphometric approach. *Kidney Int*, 2005. 67: 1595.
<https://www.ncbi.nlm.nih.gov/pubmed/15780116>
55. Munivenkatappa, R.B., *et al.* The Maryland aggregate pathology index: a deceased donor kidney biopsy scoring system for predicting graft failure. *Am J Transplant*, 2008. 8: 2316.
<https://www.ncbi.nlm.nih.gov/pubmed/18801024>
56. Liapis, H., *et al.* Banff Histopathological Consensus Criteria for Preimplantation Kidney Biopsies. *Am J Transplant*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27333454>
57. Haas, M. Donor kidney biopsies: pathology matters, and so does the pathologist. *Kidney Int*, 2014. 85: 1016.
<https://www.ncbi.nlm.nih.gov/pubmed/24786876>
58. Azancot, M.A., *et al.* The reproducibility and predictive value on outcome of renal biopsies from expanded criteria donors. *Kidney Int*, 2014. 85: 1161.
<https://www.ncbi.nlm.nih.gov/pubmed/24284518>
59. Haas, M., *et al.* Arteriosclerosis in kidneys from healthy live donors: comparison of wedge and needle core perioperative biopsies. *Arch Pathol Lab Med*, 2008. 132: 37.
<https://www.ncbi.nlm.nih.gov/pubmed/18181671>
60. Mazzucco, G., *et al.* The reliability of pre-transplant donor renal biopsies (PTDB) in predicting the kidney state. A comparative single-centre study on 154 untransplanted kidneys. *Nephrol Dial Transplant*, 2010. 25: 3401.
<https://www.ncbi.nlm.nih.gov/pubmed/20356979>
61. Wang, H.J., *et al.* On the influence of sample size on the prognostic accuracy and reproducibility of renal transplant biopsy. *Nephrol Dial Transplant*, 1998. 13: 165.
<https://www.ncbi.nlm.nih.gov/pubmed/9481734>

62. Yushkov, Y., *et al.* Optimized technique in needle biopsy protocol shown to be of greater sensitivity and accuracy compared to wedge biopsy. *Transplant Proc*, 2010. 42: 2493.
<https://www.ncbi.nlm.nih.gov/pubmed/20832530>
63. Muruve, N.A., *et al.* Are wedge biopsies of cadaveric kidneys obtained at procurement reliable? *Transplantation*, 2000. 69: 2384.
<https://www.ncbi.nlm.nih.gov/pubmed/10868645>
64. Randhawa, P. Role of donor kidney biopsies in renal transplantation. *Transplantation*, 2001. 71: 1361.
<https://www.ncbi.nlm.nih.gov/pubmed/11391219>
65. Bago-Horvath, Z., *et al.* The cutting (w)edge--comparative evaluation of renal baseline biopsies obtained by two different methods. *Nephrol Dial Transplant*, 2012. 27: 3241.
<https://www.ncbi.nlm.nih.gov/pubmed/22492825>
66. Jankovic, Z. Anaesthesia for living-donor renal transplant. *Curr Anaesth Crit Care*, 2008. 19: 175.
<http://www.sciencedirect.com/science/article/pii/S0953711207001123>
67. Karmarkar, S., *et al.* Kidney Transplantation. *Anaesth Intens Care Med* 2009. 10.5. [No abstract available].
68. Abramowicz, D., *et al.* European Renal Best Practice Guideline on kidney donor and recipient evaluation and perioperative care. *Nephrol Dial Transplant*, 2015. 30: 1790.
<https://www.ncbi.nlm.nih.gov/pubmed/25007790>
69. Schmidt, S.C., *et al.* Laparoscopic-assisted placement of peritoneal dialysis catheters: Implantation technique and results. *J Laparosc Adv Surg Tech*, 2007. 17.
<http://online.liebertpub.com/doi/pdf/10.1089/lap.2006.0162>
70. Van Loo, A.A., *et al.* Pretransplantation hemodialysis strategy influences early renal graft function. *J Am Soc Nephrol*, 1998. 9: 473.
<https://www.ncbi.nlm.nih.gov/pubmed/9513911>
71. Task Force for Preoperative Cardiac Risk, *et al.* Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery. *Eur Heart J*, 2009. 30: 2769.
<https://www.ncbi.nlm.nih.gov/pubmed/19713421>
72. Douketis, J.D., *et al.* Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 2012. 141. [No abstract available].
73. Benahmed, A., *et al.* Ticlopidine and clopidogrel, sometimes combined with aspirin, only minimally increase the surgical risk in renal transplantation: A case-control study. *Nephrol Dial Transplant*, 2014. 29: 463.
<https://www.ncbi.nlm.nih.gov/pubmed/24275542>
74. Osman, Y., *et al.* Necessity of Routine Postoperative Heparinization in Non-Risky Live-Donor Renal Transplantation: Results of a Prospective Randomized Trial. *Urology*, 2007. 69: 647.
<https://www.ncbi.nlm.nih.gov/pubmed/17445644>
75. Orlando, G., *et al.* One-shot versus multidose perioperative antibiotic prophylaxis after kidney transplantation: a randomized, controlled clinical trial. *Surgery*, 2015. 157: 104.
<https://www.ncbi.nlm.nih.gov/pubmed/25304836>
76. Choi, S.U., *et al.* Clinical significance of prophylactic antibiotics in renal transplantation. *Transplant Proc*, 2013. 45: 1392.
<https://www.ncbi.nlm.nih.gov/pubmed/23726580>
77. O'Malley, C.M., *et al.* A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg*, 2005. 100: 1518.
<https://www.ncbi.nlm.nih.gov/pubmed/15845718>
78. Othman, M.M., *et al.* The impact of timing of maximal crystalloid hydration on early graft function during kidney transplantation. *Anesth Analg*, 2010. 110: 1440.
<https://www.ncbi.nlm.nih.gov/pubmed/20418304>
79. Dalton, R.S., *et al.* Physiologic impact of low-dose dopamine on renal function in the early post renal transplant period. *Transplantation*, 2005. 79: 1561.
<https://www.ncbi.nlm.nih.gov/pubmed/15940046>
80. Ciapetti, M., *et al.* Low-dose dopamine in kidney transplantation. *Transplant Proc*, 2009. 41: 4165.
<https://www.ncbi.nlm.nih.gov/pubmed/20005360>
81. Hanif, F., *et al.* Outcome of renal transplantation with and without intra-operative diuretics. *Int J Surg*, 2011. 9: 460.
<https://www.ncbi.nlm.nih.gov/pubmed/21600319>
82. Valeriani, G., *et al.* Bench surgery in right kidney transplantation. *Transplant Proc*, 2010. 42: 1120.
<https://www.ncbi.nlm.nih.gov/pubmed/20534239>

83. Chedid, M.F., *et al.* Living donor kidney transplantation using laparoscopically procured multiple renal artery kidneys and right kidneys. *J Am Coll Surg*, 2013. 217: 144.
<https://www.ncbi.nlm.nih.gov/pubmed/23791283>
84. Phelan, P.J., *et al.* Left versus right deceased donor renal allograft outcome. *Transpl Int*, 2009. 22: 1159.
<https://www.ncbi.nlm.nih.gov/pubmed/19891044>
85. Ozdemir-van Brunschot, D.M., *et al.* Is the Reluctance for the Implantation of Right Donor Kidneys Justified? *World J Surg*, 2016. 40: 471.
<https://www.ncbi.nlm.nih.gov/pubmed/26319261>
86. Vacher-Coponat, H., *et al.* Inferior early posttransplant outcomes for recipients of right versus left deceased donor kidneys: an ANZDATA registry analysis. *Am J Transplant*, 2013. 13: 399.
<https://www.ncbi.nlm.nih.gov/pubmed/23167971>
87. Khalil, A., *et al.* Trends and outcomes in right vs. left living donor nephrectomy: an analysis of the OPTN/UNOS database of donor and recipient outcomes--should we be doing more right-sided nephrectomies? *Clin Transplant*, 2016. 30: 145.
<https://www.ncbi.nlm.nih.gov/pubmed/26589133>
88. Hsu, J.W., *et al.* Increased early graft failure in right-sided living donor nephrectomy. *Transplantation*, 2011. 91: 108.
<https://www.ncbi.nlm.nih.gov/pubmed/21441855>
89. Wang, K., *et al.* Right Versus Left Laparoscopic Living-Donor Nephrectomy: A Meta-Analysis. *Exp Clin Transplant*, 2015. 13: 214.
<https://www.ncbi.nlm.nih.gov/pubmed/26086831>
90. Ciudin, A., *et al.* Transposition of iliac vessels in implantation of right living donor kidneys. *Transplant Proc*, 2012. 44: 2945.
<https://www.ncbi.nlm.nih.gov/pubmed/23195003>
91. Feng, J.Y., *et al.* Renal vein lengthening using gonadal vein reduces surgical difficulty in living-donor kidney transplantation. *World J Surg*, 2012. 36: 468.
<https://www.ncbi.nlm.nih.gov/pubmed/21882021>
92. Nghiem, D.D. Use of spiral vein graft in living donor renal transplantation. *Clin Transplant*, 2008. 22: 719.
<https://www.ncbi.nlm.nih.gov/pubmed/18673376>
93. Matheus, W.E., *et al.* Kidney transplant anastomosis: internal or external iliac artery? *Urol J*, 2009. 6: 260.
<https://www.ncbi.nlm.nih.gov/pubmed/20027554>
94. El-Sherbiny, M., *et al.* The use of the inferior epigastric artery for accessory lower polar artery revascularization in live donor renal transplantation. *Int Urol Nephrol*, 2008. 40: 283.
<https://www.ncbi.nlm.nih.gov/pubmed/17721826>
95. Firmin, L.C., *et al.* The use of explanted internal iliac artery grafts in renal transplants with multiple arteries. *Transplantation*, 2010. 89: 766.
<https://www.ncbi.nlm.nih.gov/pubmed/20308866>
96. Oertl, A.J., *et al.* Saphenous vein interposition as a salvage technique for complex vascular situations during renal transplantation. *Transplant Proc*, 2007. 39: 140.
<https://www.ncbi.nlm.nih.gov/pubmed/17275492>
97. Tozzi, M., *et al.* Treatment of aortoiliac occlusive or dilatative disease concomitant with kidney transplantation: how and when? *Int J Surg*, 2013. 11 Suppl 1: S115.
<https://www.ncbi.nlm.nih.gov/pubmed/24380542>
98. Franchin, M., *et al.* ePTFE suture is an effective tool for vascular anastomosis in kidney transplantation. *Ital J Vasc Endovasc Surg*, 2015. 22: 61.
<http://www.minervamedica.it/en/journals/vascular-endovascular-surgery/article.php?cod=R46Y2015N02A0061>
99. Izquierdo, L., *et al.* Third and fourth kidney transplant: still a reasonable option. *Transplant Proc*, 2010. 42: 2498.
<https://www.ncbi.nlm.nih.gov/pubmed/20832531>
100. Blanco, M., *et al.* Third kidney transplantation: a permanent medical-surgical challenge. *Transplant Proc*, 2009. 41: 2366.
<https://www.ncbi.nlm.nih.gov/pubmed/19715921>
101. Nourbala, M.H., *et al.* Our experience with third renal transplantation: results, surgical techniques and complications. *Int J Urol*, 2007. 14: 1057.
<https://www.ncbi.nlm.nih.gov/pubmed/18036037>

102. Musquera, M., *et al.* Orthotopic kidney transplantation: an alternative surgical technique in selected patients. *Eur Urol*, 2010. 58: 927.
<https://www.ncbi.nlm.nih.gov/pubmed/20888120>
103. McCulloch, P., *et al.* IDEAL framework for surgical innovation 1: the idea and development stages. *BMJ*, 2013. 346: f3012.
<https://www.ncbi.nlm.nih.gov/pubmed/23778427>
104. Basu, A., *et al.* Adult dual kidney transplantation. *Current Opinion in Organ Transplantation*, 2007. 12: 379. [No abstract available].
105. Haider, H.H., *et al.* Dual kidney transplantation using midline extraperitoneal approach: description of a technique. *Transplant Proc*, 2007. 39: 1118.
<https://www.ncbi.nlm.nih.gov/pubmed/17524907>
106. Ekser, B., *et al.* Technical aspects of unilateral dual kidney transplantation from expanded criteria donors: experience of 100 patients. *Am J Transplant*, 2010. 10: 2000.
<https://www.ncbi.nlm.nih.gov/pubmed/20636454>
107. Nghiem, D.D. Simultaneous double adult kidney transplantation using single arterial and venous anastomoses. *Urology*, 2006. 67: 1076.
<https://www.ncbi.nlm.nih.gov/pubmed/16581114>
108. Veroux, P., *et al.* Two-as-one monolateral dual kidney transplantation. *Urology*, 2011. 77: 227.
<https://www.ncbi.nlm.nih.gov/pubmed/20399490>
109. Salehipour, M., *et al.* En-bloc Transplantation: an Eligible Technique for Unilateral Dual Kidney Transplantation. *Int J Organ Transplant Med*, 2012. 3: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/25013633>
110. Rigotti, P., *et al.* A single-center experience with 200 dual kidney transplantations. *Clin Transplant*, 2014. 28: 1433.
<https://www.ncbi.nlm.nih.gov/pubmed/25297945>
111. Al-Shraideh, Y., *et al.* Single vs dual (en bloc) kidney transplants from donors \leq 5 years of age: A single center experience. *World J Transplant*, 2016. 6: 239.
<https://www.ncbi.nlm.nih.gov/pubmed/27011923>
112. Alberts, V.P., *et al.* Ureterovesical anastomotic techniques for kidney transplantation: a systematic review and meta-analysis. *Transpl Int*, 2014. 27: 593.
<https://www.ncbi.nlm.nih.gov/pubmed/24606191>
113. Slagt, I.K., *et al.* A randomized controlled trial comparing intravesical to extravesical ureteroneocystostomy in living donor kidney transplantation recipients. *Kidney Int*, 2014. 85: 471.
<https://www.ncbi.nlm.nih.gov/pubmed/24284515>
114. Dadkhah, F., *et al.* Modified ureteroneocystostomy in kidney transplantation to facilitate endoscopic management of subsequent urological complications. *Int Urol Nephrol*, 2010. 42: 285.
<https://www.ncbi.nlm.nih.gov/pubmed/19760513>
115. Timsit, M.O., *et al.* Should routine pyeloureterostomy be advocated in adult kidney transplantation? A prospective study of 283 recipients. *J Urol*, 2010. 184: 2043.
<https://www.ncbi.nlm.nih.gov/pubmed/20850818>
116. Kehinde, E.O., *et al.* Complications associated with using nonabsorbable sutures for ureteroneocystostomy in renal transplant operations. *Transplant Proc*, 2000. 32: 1917.
<https://www.ncbi.nlm.nih.gov/pubmed/11119999>
117. Wilson, C.H., *et al.* Routine intraoperative ureteric stenting for kidney transplant recipients. *Cochrane Database Syst Rev*, 2013: CD004925.
<https://www.ncbi.nlm.nih.gov/pubmed/16235385>
118. Tavakoli, A., *et al.* Impact of stents on urological complications and health care expenditure in renal transplant recipients: results of a prospective, randomized clinical trial. *J Urol*, 2007. 177: 2260.
<https://www.ncbi.nlm.nih.gov/pubmed/17509336>
119. Heidari, M., *et al.* Transplantation of kidneys with duplicated ureters. *Scand J Urol Nephrol*, 2010. 44: 337.
<https://www.ncbi.nlm.nih.gov/pubmed/20653492>
120. Alberts, V.P., *et al.* Duplicated ureters and renal transplantation: a case-control study and review of the literature. *Transplant Proc*, 2013. 45: 3239.
<https://www.ncbi.nlm.nih.gov/pubmed/24182792>
121. Surange, R.S., *et al.* Kidney transplantation into an ileal conduit: a single center experience of 59 cases. *J Urol*, 2003. 170: 1727.
<https://www.ncbi.nlm.nih.gov/pubmed/14532763>

122. Kortram, K., *et al.* Perioperative Events and Complications in Minimally Invasive Live Donor Nephrectomy: A Systematic Review and Meta-Analysis. *Transplantation*, 2016. <https://www.ncbi.nlm.nih.gov/pubmed/27428715>
123. Segev, D.L., *et al.* Perioperative mortality and long-term survival following live kidney donation. *JAMA*, 2010. 303: 959. <https://www.ncbi.nlm.nih.gov/pubmed/20215610>
124. Chu, K.H., *et al.* Long-term outcomes of living kidney donors: a single centre experience of 29 years. *Nephrology (Carlton)*, 2012. 17: 85. <https://www.ncbi.nlm.nih.gov/pubmed/21919999>
125. Fehrman-Ekholm, I., *et al.* Post-nephrectomy development of renal function in living kidney donors: a cross-sectional retrospective study. *Nephrol Dial Transplant*, 2011. 26: 2377. <https://www.ncbi.nlm.nih.gov/pubmed/21459783>
126. Ibrahim, H.N., *et al.* Long-term consequences of kidney donation. *N Engl J Med*, 2009. 360: 459. <https://www.ncbi.nlm.nih.gov/pubmed/19179315>
127. Li, S.S., *et al.* A meta-analysis of renal outcomes in living kidney donors. *Medicine (Baltimore)*, 2016. 95: e3847. <https://www.ncbi.nlm.nih.gov/pubmed/27310964>
128. Gross, C.R., *et al.* Health-related quality of life in kidney donors from the last five decades: results from the RELIVE study. *Am J Transplant*, 2013. 13: 2924. <https://www.ncbi.nlm.nih.gov/pubmed/24011252>
129. Lorenz, E.C., *et al.* The impact of urinary tract infections in renal transplant recipients. *Kidney Int*, 2010. 78: 719. <https://www.ncbi.nlm.nih.gov/pubmed/20877371>
130. Ariza-Heredia, E.J., *et al.* Urinary tract infections in kidney transplant recipients: role of gender, urologic abnormalities, and antimicrobial prophylaxis. *Ann Transplant*, 2013. 18: 195. <https://www.ncbi.nlm.nih.gov/pubmed/23792521>
131. Chang, C.Y., *et al.* Urological manifestations of BK polyomavirus in renal transplant recipients. *Can J Urol*, 2005. 12: 2829. <https://www.ncbi.nlm.nih.gov/pubmed/16274519>
132. Hwang, J.K., *et al.* Comparative analysis of ABO-incompatible living donor kidney transplantation with ABO-compatible grafts: a single-center experience in Korea. *Transplant Proc*, 2013. 45: 2931. <https://www.ncbi.nlm.nih.gov/pubmed/24157006>
133. Habicht, A., *et al.* Increase of infectious complications in ABO-incompatible kidney transplant recipients--a single centre experience. *Nephrol Dial Transplant*, 2011. 26: 4124. <https://www.ncbi.nlm.nih.gov/pubmed/21622990>
134. Sorto, R., *et al.* Risk factors for urinary tract infections during the first year after kidney transplantation. *Transplant Proc*, 2010. 42: 280. <https://www.ncbi.nlm.nih.gov/pubmed/20172330>
135. Thrasher, J.B., *et al.* Extravesical versus Leadbetter-Politano ureteroneocystostomy: a comparison of urological complications in 320 renal transplants. *J Urol*, 1990. 144: 1105. <https://www.ncbi.nlm.nih.gov/pubmed/2231880>
136. Mangus, R.S., *et al.* Stented versus nonstented extravesical ureteroneocystostomy in renal transplantation: a metaanalysis. *Am J Transplant*, 2004. 4: 1889. <https://www.ncbi.nlm.nih.gov/pubmed/15476491>
137. Wilson, C.H., *et al.* Routine intraoperative ureteric stenting for kidney transplant recipients. *Cochrane Database Syst Rev*, 2005: CD004925. <https://www.ncbi.nlm.nih.gov/pubmed/16235385>
138. Osman, Y., *et al.* Routine insertion of ureteral stent in live-donor renal transplantation: is it worthwhile? *Urology*, 2005. 65: 867. <https://www.ncbi.nlm.nih.gov/pubmed/15882713>
139. Georgiev, P., *et al.* Routine stenting reduces urologic complications as compared with stenting "on demand" in adult kidney transplantation. *Urology*, 2007. 70: 893. <https://www.ncbi.nlm.nih.gov/pubmed/17919691>
140. Akoh, J.A., *et al.* Effect of ureteric stents on urological infection and graft function following renal transplantation. *World J Transplant*, 2013. 3: 1. <https://www.ncbi.nlm.nih.gov/pubmed/24175202>
141. Fayek, S.A., *et al.* Ureteral stents are associated with reduced risk of ureteral complications after kidney transplantation: a large single center experience. *Transplantation*, 2012. 93: 304. <https://www.ncbi.nlm.nih.gov/pubmed/22179401>

142. Dimitroulis, D., *et al.* Vascular complications in renal transplantation: a single-center experience in 1367 renal transplantations and review of the literature. *Transplant Proc*, 2009. 41: 1609.
<https://www.ncbi.nlm.nih.gov/pubmed/19545690>
143. Pawlicki, J., *et al.* Risk factors for early hemorrhagic and thrombotic complications after kidney transplantation. *Transplant Proc*, 2011. 43: 3013.
<https://www.ncbi.nlm.nih.gov/pubmed/21996213>
144. Rouviere, O., *et al.* Acute thrombosis of renal transplant artery: graft salvage by means of intra-arterial fibrinolysis. *Transplantation*, 2002. 73: 403.
<https://www.ncbi.nlm.nih.gov/pubmed/11884937>
145. Domagala, P., *et al.* Complications of transplantation of kidneys from expanded-criteria donors. *Transplant Proc*, 2009. 41: 2970.
<https://www.ncbi.nlm.nih.gov/pubmed/19857652>
146. Giustacchini, P., *et al.* Renal vein thrombosis after renal transplantation: an important cause of graft loss. *Transplant Proc*, 2002. 34: 2126.
<https://www.ncbi.nlm.nih.gov/pubmed/12270338>
147. Wuthrich, R.P. Factor V Leiden mutation: potential thrombogenic role in renal vein, dialysis graft and transplant vascular thrombosis. *Curr Opin Nephrol Hypertens*, 2001. 10: 409.
<https://www.ncbi.nlm.nih.gov/pubmed/11342806>
148. Parajuli, S., *et al.* Hypercoagulability in Kidney Transplant Recipients. *Transplantation*, 2016. 100: 719.
<https://www.ncbi.nlm.nih.gov/pubmed/26413991>
149. Granata, A., *et al.* Renal transplant vascular complications: the role of Doppler ultrasound. *J Ultrasound*, 2015. 18: 101.
<https://www.ncbi.nlm.nih.gov/pubmed/26191097>
150. Hogan, J.L., *et al.* Late-onset renal vein thrombosis: A case report and review of the literature. *Int J Surg Case Rep*, 2015. 6C: 73.
<https://www.ncbi.nlm.nih.gov/pubmed/25528029>
151. Hurst, F.P., *et al.* Incidence, predictors and outcomes of transplant renal artery stenosis after kidney transplantation: analysis of USRDS. *Am J Nephrol*, 2009. 30: 459.
<https://www.ncbi.nlm.nih.gov/pubmed/19776559>
152. Willicombe, M., *et al.* Postanastomotic transplant renal artery stenosis: association with *de novo* class II donor-specific antibodies. *Am J Transplant*, 2014. 14: 133.
<https://www.ncbi.nlm.nih.gov/pubmed/24354873>
153. Ghazanfar, A., *et al.* Management of transplant renal artery stenosis and its impact on long-term allograft survival: a single-centre experience. *Nephrol Dial Transplant*, 2011. 26: 336.
<https://www.ncbi.nlm.nih.gov/pubmed/20601365>
154. Seratnaehai, A., *et al.* Management of transplant renal artery stenosis. *Angiology*, 2011. 62: 219.
<https://www.ncbi.nlm.nih.gov/pubmed/20682611>
155. Rountas, C., *et al.* Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD-enhanced MR angiography, and digital subtraction angiography. *Ren Fail*, 2007. 29: 295.
<https://www.ncbi.nlm.nih.gov/pubmed/17497443>
156. Fervenza, F.C., *et al.* Renal artery stenosis in kidney transplants. *Am J Kidney Dis*, 1998. 31: 142.
<https://www.ncbi.nlm.nih.gov/pubmed/9428466>
157. Bach, D., *et al.* Percutaneous renal biopsy: three years of experience with the biopsy gun in 761 cases--a survey of results and complications. *Int Urol Nephrol*, 1999. 31: 15.
<https://www.ncbi.nlm.nih.gov/pubmed/10408297>
158. Loffroy, R., *et al.* Management of post-biopsy renal allograft arteriovenous fistulas with selective arterial embolization: immediate and long-term outcomes. *Clin Radiol*, 2008. 63: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/18455557>
159. Atray, N.K., *et al.* Post transplant lymphocele: a single centre experience. *Clin Transplant*, 2004. 18 Suppl 12: 46.
<https://www.ncbi.nlm.nih.gov/pubmed/15217407>
160. Ulrich, F., *et al.* Symptomatic lymphoceles after kidney transplantation - multivariate analysis of risk factors and outcome after laparoscopic fenestration. *Clin Transplant*, 2010. 24: 273.
<https://www.ncbi.nlm.nih.gov/pubmed/19719727>
161. Lucewicz, A., *et al.* Management of primary symptomatic lymphocele after kidney transplantation: a systematic review. *Transplantation*, 2011. 92: 663.
<https://www.ncbi.nlm.nih.gov/pubmed/21849931>

162. Capocasale, E., *et al.* Octreotide in the treatment of lymphorrhea after renal transplantation: a preliminary experience. *Transplant Proc*, 2006. 38: 1047.
<https://www.ncbi.nlm.nih.gov/pubmed/16757259>
163. Kayler, L., *et al.* Kidney transplant ureteroneocystostomy techniques and complications: review of the literature. *Transplant Proc*, 2010. 42: 1413.
<https://www.ncbi.nlm.nih.gov/pubmed/20620446>
164. Secin, F.P., *et al.* Comparing Taguchi and Lich-Gregoir ureterovesical reimplantation techniques for kidney transplants. *J Urol*, 2002. 168: 926.
<https://www.ncbi.nlm.nih.gov/pubmed/12187192>
165. Dinckan, A., *et al.* Early and late urological complications corrected surgically following renal transplantation. *Transpl Int*, 2007. 20: 702.
<https://www.ncbi.nlm.nih.gov/pubmed/17511829>
166. Kumar, A., *et al.* Evaluation of the urological complications of living related renal transplantation at a single center during the last 10 years: impact of the Double-J* stent. *J Urol*, 2000. 164: 657.
<https://www.ncbi.nlm.nih.gov/pubmed/10953120>
167. Mazzucchi, E., *et al.* Primary reconstruction is a good option in the treatment of urinary fistula after kidney transplantation. *Int Braz J Urol*, 2006. 32: 398.
<https://www.ncbi.nlm.nih.gov/pubmed/16953905>
168. Davari, H.R., *et al.* Urological complications in 980 consecutive patients with renal transplantation. *Int J Urol*, 2006. 13: 1271.
<https://www.ncbi.nlm.nih.gov/pubmed/17010003>
169. Sabnis, R.B., *et al.* The development and current status of minimally invasive surgery to manage urological complications after renal transplantation. *Indian J Urol*, 2016. 32: 186.
<https://www.ncbi.nlm.nih.gov/pubmed/27555675>
170. Suttle, T., *et al.* Comparison of Urologic Complications Between Ureteroneocystostomy and Ureteroureterostomy in Renal Transplant: A Meta-Analysis. *Exp Clin Transplant*, 2016. 14: 276.
<https://www.ncbi.nlm.nih.gov/pubmed/26925612>
171. Breda, A., *et al.* Incidence of ureteral strictures after laparoscopic donor nephrectomy. *J Urol*, 2006. 176: 1065.
<https://www.ncbi.nlm.nih.gov/pubmed/16890691>
172. Helfand, B.T., *et al.* Reconstruction of late-onset transplant ureteral stricture disease. *BJU Int*, 2011. 107: 982.
<https://www.ncbi.nlm.nih.gov/pubmed/20825404>
173. Kaskarelis, I., *et al.* Ureteral complications in renal transplant recipients successfully treated with interventional radiology. *Transplant Proc*, 2008. 40: 3170.
<https://www.ncbi.nlm.nih.gov/pubmed/19010224>
174. Gabr, A.H., *et al.* Ureteral complications after hand-assisted laparoscopic living donor nephrectomy. *Transplantation*, 2014. 97: 788.
<https://www.ncbi.nlm.nih.gov/pubmed/24305639>
175. Kristo, B., *et al.* Treatment of renal transplant ureterovesical anastomotic strictures using antegrade balloon dilation with or without holmium:YAG laser endoureterotomy. *Urology*, 2003. 62: 831.
<https://www.ncbi.nlm.nih.gov/pubmed/14624903>
176. Nie, Z., *et al.* Comparison of urological complications with primary ureteroureterostomy versus conventional ureteroneocystostomy. *Clin Transplant*, 2010. 24: 615.
<https://www.ncbi.nlm.nih.gov/pubmed/19925475>
177. Chaykovska, L., *et al.* Kidney transplantation into urinary conduits with ureteroureterostomy between transplant and native ureter: single-center experience. *Urology*, 2009. 73: 380.
<https://www.ncbi.nlm.nih.gov/pubmed/19022489>
178. Jung, G.O., *et al.* Clinical significance of posttransplantation vesicoureteral reflux during short-term period after kidney transplantation. *Transplant Proc*, 2008. 40: 2339.
<https://www.ncbi.nlm.nih.gov/pubmed/18790229>
179. Giral, M., *et al.* Acute graft pyelonephritis and long-term kidney allograft outcome. *Kidney Int*, 2002. 61: 1880.
<https://www.ncbi.nlm.nih.gov/pubmed/11967040>
180. Pichler, R., *et al.* Endoscopic application of dextranomer/hyaluronic acid copolymer in the treatment of vesico-ureteric reflux after renal transplantation. *BJU Int*, 2011. 107: 1967.
<https://www.ncbi.nlm.nih.gov/pubmed/21059169>
181. Abbott, K.C., *et al.* Hospitalized nephrolithiasis after renal transplantation in the United States. *Am J Transplant*, 2003. 3: 465.
<https://www.ncbi.nlm.nih.gov/pubmed/12694070>

182. Verrier, C., *et al.* Decrease in and management of urolithiasis after kidney transplantation. *J Urol*, 2012. 187: 1651.
<https://www.ncbi.nlm.nih.gov/pubmed/22425102>
183. Oliveira, M., *et al.* Percutaneous nephrolithotomy in renal transplants: a safe approach with a high stone-free rate. *Int Urol Nephrol*, 2011. 43: 329.
<https://www.ncbi.nlm.nih.gov/pubmed/20848196>
184. Silva, A., *et al.* Risk factors for urinary tract infection after renal transplantation and its impact on graft function in children and young adults. *J Urol*, 2010. 184: 1462.
<https://www.ncbi.nlm.nih.gov/pubmed/20727542>
185. Challacombe, B., *et al.* Multimodal management of urolithiasis in renal transplantation. *BJU Int*, 2005. 96: 385.
<https://www.ncbi.nlm.nih.gov/pubmed/16042735>
186. Basiri, A., *et al.* Ureteroscopic management of urological complications after renal transplantation. *Scand J Urol Nephrol*, 2006. 40: 53.
<https://www.ncbi.nlm.nih.gov/pubmed/16452057>
187. Roine, E., *et al.* Targeting risk factors for impaired wound healing and wound complications after kidney transplantation. *Transplant Proc*, 2010. 42: 2542.
<https://www.ncbi.nlm.nih.gov/pubmed/20832540>
188. Yannam, G.R., *et al.* Experience of laparoscopic incisional hernia repair in kidney and/or pancreas transplant recipients. *Am J Transplant*, 2011. 11: 279.
<https://www.ncbi.nlm.nih.gov/pubmed/21272235>
189. Tait, B.D., *et al.* Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. *Transplantation*, 2013. 95: 19.
<https://www.ncbi.nlm.nih.gov/pubmed/23238534>
190. European Renal Best Practice Transplantation Guideline Development Group. ERBP Guideline on the Management and Evaluation of the Kidney Donor and Recipient. *Nephrol Dial Transplant*, 2013. 28 Suppl 2: ii1.
<https://www.ncbi.nlm.nih.gov/pubmed/24026881>
191. Poulton, K., *et al.* British Transplantation Society. Guidelines for the detection of clinically relevant antibodies in allotransplantation. 2014.
http://www.bshi.org.uk/BSHI_BTS_Ab_Guidelines_Revision_June_2014.pdf
192. UNOS. United Network For Organ Sharing Website:
<https://www.unos.org/>
193. Heidt, S., Eurotransplant Manual version 3.1 Chapter 10 Histocompatibility. 2015.
https://www.eurotransplant.org/cms/mediaobject.php?file=chapter10_histocompatibility8.pdf
194. European Federation for Immunogenetics, EFI Standards for Histocompatibility and Immunogenetics Testing Version 6.3. 2015.
<http://www.efiweb.eu/efi-committees/standards-committee.html>
195. De Meester, J., *et al.* Renal transplantation of highly sensitised patients via prioritised renal allocation programs. Shorter waiting time and above-average graft survival. *Nephron*, 2002. 92: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/12187093>
196. Susal, C., *et al.* Algorithms for the determination of unacceptable HLA antigen mismatches in kidney transplant recipients. *Tissue Antigens*, 2013. 82: 83.
<https://www.ncbi.nlm.nih.gov/pubmed/23718733>
197. Bohmig, G.A., *et al.* Strategies to overcome the ABO barrier in kidney transplantation. *Nat Rev Nephrol*, 2015. 11: 732.
<https://www.ncbi.nlm.nih.gov/pubmed/26324199>
198. Zschiedrich, S., *et al.* An update on ABO-incompatible kidney transplantation. *Transpl Int*, 2015. 28: 387.
<https://www.ncbi.nlm.nih.gov/pubmed/25387763>
199. Higgins, R.M., *et al.* Antibody-incompatible kidney transplantation in 2015 and beyond. *Nephrol Dial Transplant*, 2015. 30: 1972.
<https://www.ncbi.nlm.nih.gov/pubmed/25500804>
200. Wongsaroj, P., *et al.* Modern approaches to incompatible kidney transplantation. *World J Nephrol*, 2015. 4: 354.
<https://www.ncbi.nlm.nih.gov/pubmed/26167458>
201. Bamoulid, J., *et al.* Immunosuppression and Results in Renal Transplantation. *European Urology Supplements*, 2016. 15: 415.
<https://www.ncbi.nlm.nih.gov/pubmed/25752992>

202. Kidney Disease Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*, 2009. 9 Suppl 3: S1.
<https://www.ncbi.nlm.nih.gov/pubmed/19845597>
203. Bamouid, J., *et al.* The need for minimization strategies: current problems of immunosuppression. *Transpl Int*, 2015. 28: 891.
<https://www.ncbi.nlm.nih.gov/pubmed/25752992>
204. Jones-Hughes, T., *et al.* Immunosuppressive therapy for kidney transplantation in adults: a systematic review and economic model. *Health Technol Assess*, 2016. 20: 1.
<https://www.ncbi.nlm.nih.gov/pubmed/27578428>
205. Leas, B.F., *et al.*, in *Calcineurin Inhibitors for Renal Transplant*. 2016: Rockville (MD).
206. Sawinski, D., *et al.* Calcineurin Inhibitor Minimization, Conversion, Withdrawal, and Avoidance Strategies in Renal Transplantation: A Systematic Review and Meta-Analysis. *Am J Transplant*, 2016. 16: 2117.
<https://www.ncbi.nlm.nih.gov/pubmed/26990455>
207. Webster, A.C., *et al.* Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ*, 2005. 331: 810.
<https://www.ncbi.nlm.nih.gov/pubmed/16157605>
208. Caillard, S., *et al.* Advagraf((R)) , a once-daily prolonged release tacrolimus formulation, in kidney transplantation: literature review and guidelines from a panel of experts. *Transpl Int*, 2016. 29: 860.
<https://www.ncbi.nlm.nih.gov/pubmed/26373896>
209. McCormack, P.L. Extended-release tacrolimus: a review of its use in *de novo* kidney transplantation. *Drugs*, 2014. 74: 2053.
<https://www.ncbi.nlm.nih.gov/pubmed/25352392>
210. Molnar, A.O., *et al.* Generic immunosuppression in solid organ transplantation: systematic review and meta-analysis. *BMJ*, 2015. 350: h3163.
<https://www.ncbi.nlm.nih.gov/pubmed/26101226>
211. Staatz, C.E., *et al.* Clinical Pharmacokinetics of Once-Daily Tacrolimus in Solid-Organ Transplant Patients. *Clin Pharmacokinet*, 2015. 54: 993.
<https://www.ncbi.nlm.nih.gov/pubmed/26038096>
212. van Gelder, T., *et al.* European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. *Transpl Int*, 2011. 24: 1135.
<https://www.ncbi.nlm.nih.gov/pubmed/22032583>
213. Diekmann, F. Immunosuppressive minimization with mTOR inhibitors and belatacept. *Transpl Int*, 2015. 28: 921.
<https://www.ncbi.nlm.nih.gov/pubmed/25959589>
214. Kamar, N., *et al.* Calcineurin inhibitor-sparing regimens based on mycophenolic acid after kidney transplantation. *Transpl Int*, 2015. 28: 928.
<https://www.ncbi.nlm.nih.gov/pubmed/25557802>
215. Snanoudj, R., *et al.* Immunological risks of minimization strategies. *Transpl Int*, 2015. 28: 901.
<https://www.ncbi.nlm.nih.gov/pubmed/25809144>
216. Budde, K., *et al.* Enteric-coated mycophenolate sodium. *Expert Opin Drug Saf*, 2010. 9: 981.
<https://www.ncbi.nlm.nih.gov/pubmed/20795786>
217. Cooper, M., *et al.* Enteric-coated mycophenolate sodium immunosuppression in renal transplant patients: efficacy and dosing. *Transplant Rev (Orlando)*, 2012. 26: 233.
<https://www.ncbi.nlm.nih.gov/pubmed/22863029>
218. Staatz, C.E., *et al.* Pharmacology and toxicology of mycophenolate in organ transplant recipients: an update. *Arch Toxicol*, 2014. 88: 1351.
<https://www.ncbi.nlm.nih.gov/pubmed/24792322>
219. van Gelder, T., *et al.* Mycophenolate revisited. *Transpl Int*, 2015. 28: 508.
<https://www.ncbi.nlm.nih.gov/pubmed/25758949>
220. Wagner, M., *et al.* Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev*, 2015: CD007746.
<https://www.ncbi.nlm.nih.gov/pubmed/26633102>
221. Hirsch, H.H., *et al.* European perspective on human polyomavirus infection, replication and disease in solid organ transplantation. *Clin Microbiol Infect*, 2014. 20 Suppl 7: 74.
<https://www.ncbi.nlm.nih.gov/pubmed/24476010>
222. Kotton, C.N., *et al.* Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*, 2013. 96: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/23896556>

223. Le Meur, Y., *et al.* Therapeutic drug monitoring of mycophenolates in kidney transplantation: report of The Transplantation Society consensus meeting. *Transplant Rev (Orlando)*, 2011. 25: 58.
<https://www.ncbi.nlm.nih.gov/pubmed/21454067>
224. Haller, M.C., *et al.* Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev*, 2016: CD005632.
<https://www.ncbi.nlm.nih.gov/pubmed/27546100>
225. Mathis, A.S., *et al.* Calcineurin inhibitor sparing strategies in renal transplantation, part one: Late sparing strategies. *World J Transplant*, 2014. 4: 57.
<https://www.ncbi.nlm.nih.gov/pubmed/25032096>
226. Remuzzi, G., *et al.* Mycophenolate mofetil versus azathioprine for prevention of chronic allograft dysfunction in renal transplantation: the MYSS follow-up randomized, controlled clinical trial. *J Am Soc Nephrol*, 2007. 18: 1973.
<https://www.ncbi.nlm.nih.gov/pubmed/17460145>
227. Kunz, R., *et al.* Maintenance therapy with triple versus double immunosuppressive regimen in renal transplantation: a meta-analysis. *Transplantation*, 1997. 63: 386.
<https://www.ncbi.nlm.nih.gov/pubmed/9039928>
228. Halleck, F., *et al.* An evaluation of sirolimus in renal transplantation. *Expert Opin Drug Metab Toxicol*, 2012. 8: 1337.
<https://www.ncbi.nlm.nih.gov/pubmed/22928953>
229. Ventura-Aguiar, P., *et al.* Safety of mTOR inhibitors in adult solid organ transplantation. *Expert Opin Drug Saf*, 2016. 15: 303.
<https://www.ncbi.nlm.nih.gov/pubmed/26667069>
230. Witzke, O., *et al.* Everolimus immunosuppression in kidney transplantation: What is the optimal strategy? *Transplant Rev (Orlando)*, 2016. 30: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/26603484>
231. Shipkova, M., *et al.* Therapeutic Drug Monitoring of Everolimus: A Consensus Report. *Ther Drug Monit*, 2016. 38: 143.
<https://www.ncbi.nlm.nih.gov/pubmed/26982492>
232. Xie, X., *et al.* mTOR inhibitor versus mycophenolic acid as the primary immunosuppression regime combined with calcineurin inhibitor for kidney transplant recipients: a meta-analysis. *BMC Nephrol*, 2015. 16: 91.
<https://www.ncbi.nlm.nih.gov/pubmed/26126806>
233. Liefeldt, L., *et al.* Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. *Am J Transplant*, 2012. 12: 1192.
<https://www.ncbi.nlm.nih.gov/pubmed/22300538>
234. Halleck, F., *et al.* Transplantation: Sirolimus for secondary SCC prevention in renal transplantation. *Nat Rev Nephrol*, 2012. 8: 687.
<https://www.ncbi.nlm.nih.gov/pubmed/23026948>
235. Ponticelli, C., *et al.* Skin cancer in kidney transplant recipients. *J Nephrol*, 2014. 27: 385.
<https://www.ncbi.nlm.nih.gov/pubmed/24809813>
236. Liu, Y., *et al.* Basiliximab or antithymocyte globulin for induction therapy in kidney transplantation: a meta-analysis. *Transplant Proc*, 2010. 42: 1667.
<https://www.ncbi.nlm.nih.gov/pubmed/20620496>
237. Sun, Z.J., *et al.* Efficacy and Safety of Basiliximab Versus Daclizumab in Kidney Transplantation: A Meta-Analysis. *Transplant Proc*, 2015. 47: 2439.
<https://www.ncbi.nlm.nih.gov/pubmed/26518947>
238. Webster, A.C., *et al.* Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database Syst Rev*, 2010: CD003897.
<https://www.ncbi.nlm.nih.gov/pubmed/20091551>
239. Bamouid, J., *et al.* Anti-thymocyte globulins in kidney transplantation: focus on current indications and long-term immunological side effects. *Nephrol Dial Transplant*, 2016.
<https://www.ncbi.nlm.nih.gov/pubmed/27798202>
240. Malvezzi, P., *et al.* Induction by anti-thymocyte globulins in kidney transplantation: a review of the literature and current usage. *J Nephropathol*, 2015. 4: 110.
<https://www.ncbi.nlm.nih.gov/pubmed/26457257>
241. Grinyo, J.M., *et al.* Belatacept utilization recommendations: an expert position. *Expert Opin Drug Saf*, 2013. 12: 111.
<https://www.ncbi.nlm.nih.gov/pubmed/26816011>

242. Wojciechowski, D., *et al.* Current status of costimulatory blockade in renal transplantation. *Curr Opin Nephrol Hypertens*, 2016. 25: 583.
<https://www.ncbi.nlm.nih.gov/pubmed/27517137>
243. Durrbach, A., *et al.* Long-Term Outcomes in Belatacept- Versus Cyclosporine-Treated Recipients of Extended Criteria Donor Kidneys: Final Results From BENEFIT-EXT, a Phase III Randomized Study. *Am J Transplant*, 2016. 16: 3192.
<https://www.ncbi.nlm.nih.gov/pubmed/27130868>
244. Vincenti, F., *et al.* Belatacept and Long-Term Outcomes in Kidney Transplantation. *N Engl J Med*, 2016. 374: 333.
<https://www.ncbi.nlm.nih.gov/pubmed/26816011>
245. Brakemeier, S., *et al.* Experience with belatacept rescue therapy in kidney transplant recipients. *Transpl Int*, 2016. 29: 1184.
<https://www.ncbi.nlm.nih.gov/pubmed/27514317>
246. Bamouid, J., *et al.* Advances in pharmacotherapy to treat kidney transplant rejection. *Expert Opin Pharmacother*, 2015. 16: 1627.
<https://www.ncbi.nlm.nih.gov/pubmed/26159444>
247. Broecker, V., *et al.* The significance of histological diagnosis in renal allograft biopsies in 2014. *Transpl Int*, 2015. 28: 136.
<https://www.ncbi.nlm.nih.gov/pubmed/25205033>
248. Halloran, P.F., *et al.* Molecular assessment of disease states in kidney transplant biopsy samples. *Nat Rev Nephrol*, 2016. 12: 534.
<https://www.ncbi.nlm.nih.gov/pubmed/27345248>
249. Haas, M., *et al.* Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant*, 2014. 14: 272.
<https://www.ncbi.nlm.nih.gov/pubmed/24472190>
250. Morgan, T.A., *et al.* Complications of Ultrasound-Guided Renal Transplant Biopsies. *Am J Transplant*, 2016. 16: 1298.
<https://www.ncbi.nlm.nih.gov/pubmed/26601796>
251. Redfield, R.R., *et al.* Nature, timing, and severity of complications from ultrasound-guided percutaneous renal transplant biopsy. *Transpl Int*, 2016. 29: 167.
<https://www.ncbi.nlm.nih.gov/pubmed/26284692>
252. Amore, A. Antibody-mediated rejection. *Curr Opin Organ Transplant*, 2015. 20: 536.
<https://www.ncbi.nlm.nih.gov/pubmed/26348571>
253. Burton, S.A., *et al.* Treatment of antibody-mediated rejection in renal transplant patients: a clinical practice survey. *Clin Transplant*, 2015. 29: 118.
<https://www.ncbi.nlm.nih.gov/pubmed/25430052>
254. Haririan, A. Current status of the evaluation and management of antibody-mediated rejection in kidney transplantation. *Curr Opin Nephrol Hypertens*, 2015. 24: 576.
<https://www.ncbi.nlm.nih.gov/pubmed/26406806>
255. Roberts, D.M., *et al.* The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation*, 2012. 94: 775.
<https://www.ncbi.nlm.nih.gov/pubmed/23032865>
256. Sautenet, B., *et al.* One-year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation: RITUX ERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial. *Transplantation*, 2016. 100: 391.
<https://www.ncbi.nlm.nih.gov/pubmed/26555944>
257. Kamar, N., *et al.* Incidence and predictive factors for infectious disease after rituximab therapy in kidney-transplant patients. *Am J Transplant*, 2010. 10: 89.
<https://www.ncbi.nlm.nih.gov/pubmed/19656128>
258. Ejaz, N.S., *et al.* Review of bortezomib treatment of antibody-mediated rejection in renal transplantation. *Antioxid Redox Signal*, 2014. 21: 2401.
<https://www.ncbi.nlm.nih.gov/pubmed/24635140>
259. Farrugia, D., *et al.* Malignancy-related mortality following kidney transplantation is common. *Kidney Int*, 2014. 85: 1395.
<https://www.ncbi.nlm.nih.gov/pubmed/24257690>
260. Piselli, P., *et al.* Risk of *de novo* cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997-2009. *Eur J Cancer*, 2013. 49: 336.
<https://www.ncbi.nlm.nih.gov/pubmed/23062667>

261. Jardine, A.G., *et al.* Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet*, 2011. 378: 1419.
<https://www.ncbi.nlm.nih.gov/pubmed/22000138>
262. Liefeldt, L., *et al.* Risk factors for cardiovascular disease in renal transplant recipients and strategies to minimize risk. *Transpl Int*, 2010. 23: 1191.
<https://www.ncbi.nlm.nih.gov/pubmed/21059108>
263. Nankivell, B.J., *et al.* Diagnosis and prevention of chronic kidney allograft loss. *Lancet*, 2011. 378: 1428.
<https://www.ncbi.nlm.nih.gov/pubmed/22000139>
264. Boor, P., *et al.* Renal allograft fibrosis: biology and therapeutic targets. *Am J Transplant*, 2015. 15: 863.
<https://www.ncbi.nlm.nih.gov/pubmed/25691290>
265. Westall, G.P., *et al.* Antibody-mediated rejection. *Curr Opin Organ Transplant*, 2015. 20: 492.
<https://www.ncbi.nlm.nih.gov/pubmed/26262460>
266. Chapman, J.R. Chronic calcineurin inhibitor nephrotoxicity-lest we forget. *Am J Transplant*, 2011. 11: 693.
<https://www.ncbi.nlm.nih.gov/pubmed/21446974>

5. CONFLICT OF INTEREST

All members of the EAU Renal Transplantation Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: <http://www.uroweb.org/guidelines/>. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

EAU Guidelines on Thromboprophylaxis in Urological Surgery

K.A.O. Tikkinen (Chair), R. Cartwright, M.K. Gould, R. Naspro,
G. Novara, P.M. Sandset, P.D. Violette, G.H. Guyatt

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1. INTRODUCTION

1.1 Aims and objectives

Due to the hypercoagulable state induced by surgery, serious complications of urological surgery include deep vein thrombosis (DVT) and pulmonary embolism (PE) - together referred to as venous thromboembolism (VTE) - and major bleeding [1-4]. Decisions regarding pharmacologic thromboprophylaxis in urologic surgery involve a trade-off between decreased risk of (VTE) and increased risk of bleeding [1-3]. Currently, there exists substantial practice variation in the use of thromboprophylaxis in urology, both within and between countries [5-7]. This variation is unsurprising when one considers that recommendations from national and international guidelines often conflict [2].

To date, existing recommendations for thromboprophylaxis have been limited by a lack of urology-specific evidence [2]. Decisions regarding thromboprophylaxis require both estimates of relative effects on VTE and bleeding, and absolute risks of VTE and bleeding in the absence of prophylaxis (the latter is referred to as baseline risk). Substantial evidence from randomised control trials (RCTs) across a range of surgical procedures is available, and it is reasonable to assume that relative effects of prophylaxis are similar across surgical procedures. Evidence regarding baseline risk across urological procedures is, however, more limited, and systematic summaries of the available evidence have thus far been unavailable [1, 3].

To develop these guidelines, the Panel conducted systematic reviews of the baseline risk of VTE and bleeding in a wide variety of urological procedures [1, 8, 9]. These reviews provide a stronger evidence base for urological thromboprophylaxis guidelines than has been previously available.

Utilising this newly summarised evidence [8, 9], these Guidelines from the European Association of Urology (EAU) Working Panel on Thromboprophylaxis in Urological Surgery provide practical evidence-based guidance regarding post-surgery thromboprophylaxis and peri-operative management of antithrombotic agents in urology.

Clinicians who wish to implement our recommendations should bear in mind that guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to guide decisions that must also take into account patients' values and preferences as well as their individual circumstances. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines on Thromboprophylaxis in Urological Surgery Panel consists of physicians/methodologists with expertise from urology, internal medicine, haematology, gynaecology and clinical epidemiology. Although the Guidelines are written primarily for urologists, they can also be used by other physicians, patients or other interested parties.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Thromboprophylaxis in Urological Surgery Guidelines. These are abridged versions which may require consultation together with the full text version. All are available through the EAU website: <http://www.uroweb.org/guidelines/>.

1.4 Publication history

These EAU Guidelines on Thromboprophylaxis in Urological Surgery are the first of their kind.

2. METHODS

2.1 Guideline methodology

The EAU Guidelines on Thromboprophylaxis in Urological Surgery Panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessment of quality of evidence and grading of recommendations [10-12].

GRADE offers four levels of evidence quality, reflecting the degree of certainty or confidence in the evidence: high, moderate, low, and very low [11]. For relative treatment effect, RCTs are high-quality evidence

and observational studies are low-quality evidence. For baseline risk (such as risk of VTE post-surgery), observational studies are high-quality evidence. Quality may be rated down as a result of limitations in study design or implementation (risk of bias), imprecision of estimates (wide confidence intervals), inconsistency (variability in results), indirectness of evidence, or publication bias. Quality may be rated up on the basis of a very large magnitude of effect, a dose-response gradient, and if consideration of all plausible biases would reduce an apparent treatment effect, or create an effect when none is apparent. The lowest quality of any critical outcome represents the overall quality of evidence.

The strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects. GRADE classifies recommendations as strong or weak [12]. Strong recommendations mean that all or virtually all informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly. Weak recommendations mean that patients' choices will vary according to their values and preferences, and that clinicians must ensure that patients' care is in keeping with their values and preferences through shared decision-making. Strength of recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence (certainty in estimates), and nature and variability of values and preferences.

Post-operative thromboprophylaxis and peri-operative management of antithrombotic agents in urology are discussed separately. Specific methods are presented in the context of the relevant recommendations.

3. GUIDELINE

3.1 Thromboprophylaxis post-surgery

3.1.1 *Introduction*

This guideline provides procedure and patient risk-specific guidance weighing the benefit of reduced VTE with the harm of increased bleeding. The Panel provides recommendations for numerous urologic procedures with a simple and practical patient risk stratification scheme.

3.1.2 *Outcomes and definitions*

The Panel defined non-fatal and fatal symptomatic VTE and non-fatal and fatal major bleeding as key outcomes. Venous thromboembolism was defined as symptomatic DVT or PE and major bleeding was defined as bleeding requiring re-operation or intervention (such as angioembolisation). Transfusion, indwelling catheter, or change in hemoglobin levels were not considered as part of "major bleeding".

3.1.3 *Timing and duration of thromboprophylaxis*

High-quality evidence suggests that, of the cumulative risk during the first four weeks post-surgery, approximately 50% of major bleeds occur between surgery and the next morning and approximately 90% during the first four post-surgical days. In contrast, the risk of VTE is almost constant during these first four post-surgical weeks (Figure 1) [1, 13-15].

There are no direct comparisons of the same agent administered before versus after surgery. Recent studies with direct-acting oral anticoagulants (DOACs) in orthopedic surgery have, however, suggested that, relative to starting low molecular weight heparin (LMWH) before surgery, prophylaxis can begin 24 hours after surgery without an increase in VTE but with a decrease in bleeding complications [16, 17]. Given these findings, in addition to the compelling rationale regarding the relative timing of bleeds versus thrombosis (Figure 1), we recommend administration of thromboprophylaxis beginning the day after surgery.

One could argue that prophylaxis be started even later than this, especially in procedures with high bleeding risk. The extent to which an even later start would decrease the effectiveness of thromboprophylaxis is, however, open to question. Given that the further the patient is from surgery the greater the net benefit of prophylaxis (as bleeding risks decreases), while the risk of VTE is just as great in the fourth week after surgery as in the first, the optimal duration of pharmacological prophylaxis is approximately four weeks post-surgery [1, 13-15].

Figure 1: Proportion of cumulative risk (%) of VTE and major bleeding by week since surgery during the first four post-operative weeks

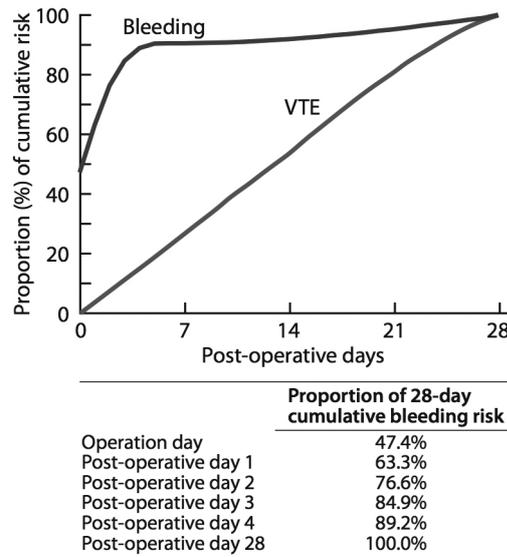


Figure modified from: Tikkinen KA, *et al.* Systematic reviews of observational studies of risk of thrombosis and bleeding in urological surgery (ROTBUS): introduction and methodology. *Syst Rev* 2014;3:150. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

3.1.4 **Basic principles for recommending (or not recommending) post-surgery thromboprophylaxis**

Considerations in the administration of thromboprophylaxis include the relative effect of prophylaxis on key outcomes, baseline risk of key outcomes, as well as patient-related risk (and protective) factors. Finally, one must consider the quality of evidence (certainty in estimates) as well as the relative importance of the relevant outcomes.

3.1.4.1 *Effect of prophylaxis on key outcomes*

The Panel performed several meta-analyses of RCTs in urology, general surgery, gynecology, and gastrointestinal surgery to inform relative risk estimates of thromboprophylaxis [1, 8, 9]. These meta-analyses demonstrated that anticoagulants (such as LMWH) reduce the relative risk of VTE by approximately 50% and increase the relative risk of major bleeding by approximately 50% [1, 8, 9]. These meta-analyses also demonstrated 50% VTE risk reduction for mechanical prophylaxis [1, 8, 9]. An earlier meta-analysis informing the risk estimates for direct-acting oral anticoagulants yielded similar estimates: a decrease in the relative risk of VTE by approximately 50% and an increase of major bleeding by approximately 50% [18]. The evidence regarding pharmacological prophylaxis was judged as high-quality but low-certainty for mechanical prophylaxis because studies used surrogate outcomes, had very few events, unblinded patients and assessors, and provided almost no information on intermittent pneumatic compression (low-quality evidence) [1, 8, 9].

3.1.4.2 *Baseline risk of key outcomes*

The Panel performed a series of systematic reviews to provide estimates of absolute risk of symptomatic VTE and bleeding requiring re-operation in urologic surgery [1, 8, 9]. The cited publications, with minor modifications, provide the evidence summary used to develop these recommendations.

3.1.4.3 *Patient-related risk (and protective) factors*

The Panel conducted a comprehensive literature search addressing VTE and bleeding risk factors in the context of urology, general surgery, gynecology, and gastro intestinal surgery [1]. A model was developed for VTE risk based on the studies reporting the most relevant and high-quality evidence [19-27] (Table 1). However, this model has not been validated and clinicians may consider other factors, including the length of the surgical procedure, oral contraception, immobility, spinal cord injury, and inheritable blood disorders such as

antiphospholipid antibody syndromes, factor V Leiden, antithrombin, protein C or S deficiencies, when making decisions. The Panel's search did not reveal studies demonstrating convincing and replicable risk factors for bleeding [1]; therefore, bleeding risk was not stratified by patient specific factors.

Table 1: Venous thromboembolism (VTE) according to patient risk factors

	Risk	Likelihood of VTE
Low risk	No risk factors	1x
Medium risk	Any one of the following: age 75 years or more; Body mass index 35 or more; VTE in 1st degree relative (parent, full sibling, or child).	2x
High risk	Prior VTE Patients with any combination of two or more risk factors	4x

3.1.4.4 From evidence to recommendations

When creating recommendations, the Panel first calculated the net benefit (absolute reduction in VTE risk – absolute increase in bleeding risk) and thereafter considered quality of evidence, separately for both pharmacological and mechanical prophylaxis. The Panel made strong recommendations only if the quality of evidence was moderate or high and net benefit fulfilled threshold criteria (see below); otherwise, the Panel made weak recommendations.

When calculating the net benefit, twice the weight was assigned for major bleeding as for 'any symptomatic VTE'. The most comprehensive guideline published in the field, the American College of Chest Physicians (ACCP) guideline on "Prevention of VTE in Nonorthopedic Surgical Patients" considered symptomatic VTE and major bleeding as having the same weight. However, they included transfusions in their definition of major bleeding [28] which the Panel considered less relevant because: 1) studies often did not report transfusions, 2) criteria for transfusion vary widely between studies, and use of transfusion may have limited relation to underlying bleeding, and 3) transfusions are less important to patients than are reoperations. Given this guideline's focus on only the more severe bleeds – those that require re-operation – the greater weight on preventing bleeding is appropriate.

For each procedure (and separately for each patient risk factor stratum), the net benefit of using pharmacological thromboprophylaxis (benefit from VTE reduction – harm from bleeding) was calculated. After considering the net benefit and quality of evidence, the thresholds presented in Table 2 were indentified.

Table 2: Thresholds of net benefit and quality of evidence used when creating recommendations

Net benefit*	Recommendation	Note
Pharmacological prophylaxis		
≥ 10 per 1000	STRONG in FAVOUR	If based on moderate or high-quality evidence
≥ 10 per 1000	WEAK in FAVOUR	If based on low or very low-quality evidence
≥ 5-10 per 1000	WEAK in FAVOUR	In borderline situations prophylaxis was always favoured as case fatality is higher for VTE than for bleeding [8, 9]
≥ 1-5 per 1000	WEAK AGAINST	
< 1 per 1000	WEAK AGAINST	If based on low or very low-quality evidence
< 1 per 1000	STRONG AGAINST	If based on moderate or high-quality evidence
Mechanical prophylaxis		
≥ 2.5 per 1000	WEAK in FAVOUR	
< 2.5 per 1000	WEAK AGAINST	

* Net benefit is equal to absolute reduction in VTE risk minus absolute increase in bleeding risk (with twice the weight for major bleeding as for VTE). The net benefit is positive when the value of reduced VTE is greater than increased bleeding.

These thresholds reflect value and preference considerations for which there is limited evidence available [29]. A recent multinational study found that the median threshold net benefit at which women with a history of VTE were willing to accept use of heparin to prevent VTE during pregnancy or the post-partum period is 30 in 1,000 [30]. In that study, the use of prophylaxis spanned the entire duration of pregnancy and continued during the

post-partum period. As post-surgery prophylaxis has a much shorter duration, and is thus less burdensome, our threshold of strong recommendation when net benefit is 10 in 1,000 or more is consistent with this evidence. As mechanical prophylaxis is typically used for a shorter duration than the Panel recommend for pharmacological prophylaxis [31], a lower threshold for mechanical prophylaxis was used.

Making a recommendation regarding thromboprophylaxis requires trading off VTE reduction against bleeding increase, and thus placing a relative value on the two events. A serious bleed (defined as bleeding requiring re-operation or intervention) was considered twice as important as a VTE (defined as symptomatic DVT or PE) event. For patients who feel very differently about this relative value judgment, the Panel's recommendations may not be optimal.

3.1.5 **General statements for all procedure-specific recommendations**

Consistent with GRADE guidance [32], a single good practice statement was made in which the supporting evidence is compelling, though indirect, and which was not summarised systematically. This association between early ambulation and decreased post-operative complications, in particular decrease in VTE, and early discharge from hospital is convincing. Further, early ambulation has no important adverse consequences. Therefore, the Panel believes that early ambulation for all patients after surgery represents good clinical practice.

The following apply to all recommendations for pharmacologic prophylaxis:

- All recommendations are based on a starting time of the morning after surgery.
- The optimal duration of prophylaxis for all recommendations is approximately four weeks post-surgery.
- There are number of acceptable alternatives for pharmacologic prophylaxis (Table 3).

Table 3: Alternative regimens for pharmacological prophylaxis

Pharmacological agent	Dosage*
Low molecular weight heparins:	
Dalteparin	5,000 IU injection once a day
Enoxaparin	40 mg injection once a day
Tinzaparin	3,500/4,500 IU injection once a day
Unfractionated heparin	5,000 IU injection two or three times a day
Fondaparinux [†]	2.5 mg injection once a day
Direct acting oral anticoagulants [†] :	
Dabigatran	220 mg tablet once a day
Apixaban	2.5 mg tablet once a day
Edoxaban	30 mg tablet once a day
Rivaroxaban	10 mg tablet once a day

* Dosages may not apply in renal impairment.

[†] Fondaparinux and direct acting oral anticoagulants have not been sufficiently studied in urology to warrant on-label use for post-surgery thromboprophylaxis.

3.1.6 **Recommendations**

Ambulatory day surgery

R1. In all patients undergoing minor ambulatory day surgery (for example, circumcision, hydrocelectomy and vasectomy), the Panel recommends against use of pharmacological prophylaxis (**strong, moderate-quality evidence**), and against use of mechanical prophylaxis (**strong, moderate-quality evidence**).

Note: The Panel is of the opinion that these patients have risk of VTE close to the general population with an increased risk of bleeding.

Open radical cystectomy

R2. In all patients undergoing open radical cystectomy, the Panel recommends use of pharmacological prophylaxis (**strong, moderate or high-quality evidence**), and suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

Robotic radical cystectomy

R3. In all patients undergoing robotic radical cystectomy, the Panel suggests use of pharmacological prophylaxis (**weak, low-quality evidence**), and suggest use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

Table 4: Procedure-specific evidence summaries with recommendations for radical cystectomies

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Cystectomy, Open	Venous thromboembolism	Low-risk	29	13	Moderate	Strong, for	Weak, for
		Medium-risk	58	27	High	Strong, for	Weak, for
		High risk	116	56	High	Strong, for	Weak, for
	Bleeding requiring reoperation		3.0		Moderate/High		
Cystectomy, Robotic	Venous thromboembolism	Low-risk	26	11	Low	Weak, for	Weak, for
		Medium-risk	52	24	Low	Weak, for	Weak, for
		High risk	103	50	Low	Weak, for	Weak, for
	Bleeding requiring reoperation		3.0		Low		

* Net benefit is equal to absolute reduction in VTE risk minus absolute increase in bleeding risk (with twice the weight for major bleeding as for VTE). For instance, in medium-risk patients undergoing open radical cystectomy, use of pharmacological prophylaxis, such as LMWH, beginning first post-surgery day for four weeks decreases absolute risk of VTE by 29 per 1,000 and increases absolute risk of bleeding by 0.8 per 1,000 (Figure 1). As twice the weight for major bleeding was assigned as for VTE, the net benefit is 27 per 1,000.

Laparoscopic radical prostatectomy

R4. For patients undergoing laparoscopic radical prostatectomy without pelvic lymph node dissection (PLND), for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (**strong, moderate-quality evidence**) and suggests against use of mechanical prophylaxis (**weak, low-quality evidence**); for those at moderate and high risk, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate or high quality evidence**) and suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R5. For patients undergoing laparoscopic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (**strong, moderate-quality evidence**); for those at medium risk, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (**strong, high-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R6. For patients undergoing laparoscopic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (**weak, high-quality evidence**); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (**strong, high-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

Open radical prostatectomy

R7. For patients undergoing open radical prostatectomy without PLND or with standard PLND, for those at low risk of VTE, the use of pharmacologic prophylaxis is suggested (**weak, moderate-quality evidence**); for those at medium and high risk, the use of pharmacologic prophylaxis is recommended (**strong, moderate or high-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R8. For all patients undergoing open radical prostatectomy with extended PLND, the Panel recommends use of pharmacologic prophylaxis (**strong, moderate or high-quality evidence**), and suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

Robotic radical prostatectomy

R9. For patients undergoing robotic radical prostatectomy without PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (**strong, moderate-quality evidence**) and suggests against use of mechanical prophylaxis (**weak, low-quality evidence**); for those at medium and high risk, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**) and suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R10. For patients undergoing robotic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (**strong, moderate-quality evidence**); for those at medium risk, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at high risk, the Panel suggests use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R11. For patients undergoing robotic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (**strong, moderate-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

Table 5: Procedure-specific evidence summaries with recommendations for radical prostatectomies

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Prostatectomy, Laparoscopic without pelvic lymph node dissection (PLND)	Venous thromboembolism	Low-risk	4.0	-1.7	Moderate	Strong - against	Weak - against
		Medium-risk	8.0	0.30	Moderate	Weak - against	Weak - for
		High-risk	15	4.0	High	Weak - against	Weak - for
	Bleeding requiring reoperation		7.0		Moderate		
Prostatectomy, Laparoscopic with standard PLND	Venous thromboembolism	Low-risk	8.0	-1.3	Moderate	Strong - against	Weak - for
		Medium-risk	15	2.2	Moderate	Weak - against	Weak - for
		High-risk	30	10	High	Strong - for	Weak - for
	Bleeding requiring reoperation		10		Moderate		
Prostatectomy, Laparoscopic with extended PLND	Venous thromboembolism	Low-risk	15	0.10	Moderate	Weak - against	Weak - for
		Medium-risk	30	7.6	High	Weak - for	Weak - for
		High-risk	60	23	High	Strong - for	Weak - for
	Bleeding requiring reoperation		14		Moderate		
Prostatectomy, Open without PLND	Venous thromboembolism	Low-risk	10	4.5	Moderate	Weak - for	Weak - for
		Medium-risk	20	9.5	Moderate	Strong - for	Weak - for
		High-risk	39	19	High	Strong - for	Weak - for
	Bleeding requiring reoperation		1.0		Moderate		

Prostatectomy, Open with standard PLND	Venous thromboembolism	Low-risk	20	8.9	Moderate	Weak - for	Weak - for
		Medium-risk	39	18	High	Strong - for	Weak - for
		High-risk	79	38	High	Strong -for	Weak - for
	Bleeding requiring reoperation		2.0		Moderate		
Prostatectomy, Open with extended PLND	Venous thromboembolism	Low-risk	39	18	Moderate	Strong - for	Weak - for
		Medium-risk	79	38	High	Strong - for	Weak - for
		High-risk	157	77	High	Strong - for	Weak - for
	Bleeding requiring reoperation		2.0		Moderate		
Prostatectomy, Robotic without PLND	Venous thromboembolism	Low-risk	2.0	-1.1	Moderate	Strong - against	Weak - against
		Medium-risk	5.0	0.40	Moderate	Weak - against	Weak - for
		High-risk	9.0	2.4	Moderate	Weak - against	Weak - for
	Bleeding requiring reoperation		4.0		Moderate		
Prostatectomy, Robotic with standard PLND	Venous thromboembolism	Low-risk	5.0	-0.7	Moderate	Strong - against	Weak - for
		Medium-risk	9.0	1.3	Moderate	Weak - against	Weak - for
		High-risk	19	6.3	Moderate	Weak - for	Weak - for
	Bleeding requiring reoperation		6.0		Moderate		
Prostatectomy, Robotic with extended PLND	Venous thromboembolism	Low-risk	9.0	0.3	Moderate	Weak - against	Weak - for
		Medium-risk	19	5.3	Moderate	Weak - for	Weak - for
		High-risk	37	14	Moderate	Strong - for	Weak - for
	Bleeding requiring reoperation		8.0		Moderate		

Nephrectomy

R12. For patients undergoing laparoscopic partial nephrectomy, for those at low and medium-risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, low-quality evidence**); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (**strong, moderate-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R13. For all patients undergoing open partial nephrectomy, the Panel suggests use of pharmacologic prophylaxis (**weak, very low-quality evidence**), and suggests use of mechanical prophylaxis until ambulation (**weak, very low-quality evidence**).

R14. For patients undergoing robotic partial nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (**strong, high-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R15. For patients undergoing laparoscopic radical nephrectomy, for those at low or medium risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low-quality evidence**); for those at high risk, the Panel suggests use of pharmacologic prophylaxis (**weak, very low-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, very low-quality evidence**).

R16. For patients undergoing open radical nephrectomy, the Panel suggests use of pharmacologic prophylaxis (**weak, very low-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R17. For all patients undergoing radical nephrectomy with thrombectomy, the Panel suggests use of pharmacologic prophylaxis (**weak, very low-quality evidence**), and suggests use of mechanical prophylaxis until ambulation (**weak, very low-quality evidence**).

R18. For all patients undergoing open nephroureterectomy, the Panel suggests use of pharmacologic prophylaxis (**weak, very low-quality evidence**), and suggests use of mechanical prophylaxis until ambulation (**weak, very low-quality evidence**).

Table 6: Procedure-specific evidence summaries with recommendations for kidney procedures for cancer

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Nephrectomy, Laparoscopic partial	Venous thromboembolism	Low-risk	11	-3.4	Low	Weak - against	Weak - for
		Medium-risk	21	1.6	Low	Weak - against	Weak - for
		High-risk	42	12	Moderate	Strong - for	Weak - for
	Bleeding requiring reoperation		17		Low/Moderate		
Nephrectomy, Open partial	Venous thromboembolism	Low-risk	10	4.5	Very low	Weak - for	Weak - for
		Medium-risk	20	9.5	Very low	Weak - for	Weak - for
		High-risk	39	19	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		1.0		Moderate		
Nephrectomy-Robotic partial	Venous thromboembolism	Low-risk	10	2.4	Moderate	Weak - against	Weak - for
		Medium-risk	19	6.9	Moderate	Weak - for	Weak - for
		High-risk	39	17	high-quality	Strong - for	Weak - for
	Bleeding requiring reoperation		5.0		Moderate		
Nephrectomy, Laparoscopic radical	Venous thromboembolism	Low-risk	7.0	0.9	Very low	Weak - against	Weak - for
		Medium-risk	13	3.9	Very low	Weak - against	Weak - for
		High-risk	26	10	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		5.0		Very low		
Nephrectomy, Open radical	Venous thromboembolism	Low-risk	11	5.2	Low	Weak - for	Weak - for
		Medium-risk	22	11	Low	Weak - for	Weak - for
		High-risk	44	22	Low	Weak - for	Weak - for
	Bleeding requiring reoperation		0.5		Very low		
Radical nephrectomy with thrombectomy	Venous thromboembolism	Low-risk	29	4.0	Very low	Weak - for	Weak - for
		Medium-risk	58	19	Very low	Weak - for	Weak - for
		High-risk	116	48	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		20		Very low		
Open nephroureterectomy	Venous thromboembolism	Low-risk	16	7.7	Very low	Weak - for	Weak - for
		Medium-risk	31	15	Very low	Weak - for	Weak - for
		High-risk	62	31	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		0.5		Very low		

R19. For all patients undergoing primary nerve sparing RPLND, the Panel suggests use of pharmacologic prophylaxis (**weak, very low-quality evidence**), and suggests use of mechanical prophylaxis until ambulation (**weak, very low-quality evidence**).

Table 7: Procedure-specific evidence summaries with recommendations for primary nerve sparing retroperitoneal lymph node dissection

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Primary nerve sparing retroperitoneal lymph node dissection	Venous thromboembolism	Low-risk	23	10	Very low	Weak - for	Weak - for
		Medium-risk	45	21			
		High-risk	91	44			
	Bleeding requiring reoperation		2.0		Very low		

Non-cancer urological procedures

R20. For all patients undergoing transurethral resection of the prostate (TURP) or equivalent procedures, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low-quality evidence**); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (**weak, low-quality evidence**); and for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, low-quality evidence**).

R21. For patients undergoing laparoscopic donor nephrectomy or open donor nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low or low-quality evidence**), and suggests against use of mechanical prophylaxis (**weak, very low or low-quality evidence**); for medium risk patients, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low or low-quality evidence**), and suggests use of mechanical prophylaxis until ambulation (**weak, very low or low-quality evidence**); and for high risk patients, the Panel suggests use of pharmacologic prophylaxis (**weak, very low or low-quality evidence**), and suggests use of mechanical prophylaxis until ambulation (**weak, very low or low-quality evidence**).

R22. For all patients undergoing open prolapse surgery or reconstructive pelvic surgery, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low-quality evidence**); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (**weak, very low or low-quality evidence**); while for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, very low or low-quality evidence**).

R23. For all patients undergoing percutaneous nephrolithotomy, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low-quality evidence**); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (**weak, very low-quality evidence**); while for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (**weak, very low-quality evidence**).

Table 8: Procedure-specific evidence summaries (with recommendations) for non-cancer procedures

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
		Low-risk	High-risk				
Transurethral resection of the prostate (TURP) or equivalent	Venous thrombo-embolism	Low-risk	2.0	-0.1	Low	Weak - against	Weak - against
		Medium-risk	4.0	0.9	Low	Weak - against	Weak - against
		High-risk	8.0	2.9	Low	Weak - against	Weak - for
	Bleeding requiring reoperation		2.0		Very low		
Donor nephrectomy, laparoscopic	Venous thrombo-embolism	Low-risk	4.0	1.5	Low	Weak - against	Weak - against
		Medium-risk	7.0	3.0	Low	Weak - against	Weak - for
		High-risk	14	6.5	Low	Weak - for	Weak - for
	Bleeding requiring reoperation		1.0		Low		
Donor nephrectomy, open	Venous thrombo-embolism	Low-risk	3.0	1.0	Very low	Weak - against	Weak - against
		Medium-risk	7.0	3.0	Very low	Weak - against	Weak - for
		High-risk	13	6.0	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		1.0		Very low		
Recipient nephrectomy, open	Venous thrombo-embolism	Low-risk	13	-5.6	Very low	Weak - against*	Weak - for
		Medium-risk	27	1.4	Very low	Weak - against*	Weak - for
		High-risk	53	14	Very low	Weak - for*	Weak - for
	Bleeding requiring reoperation		23		Very low		
Prolapse surgery, open	Venous thrombo-embolism	Low-risk	2.0	-1.1	Low	Weak - against	Weak - against
		Medium-risk	3.0	-0.6	Low	Weak - against	Weak - against
		High-risk	7.0	1.4	Low	Weak - against	Weak - for
	Bleeding requiring reoperation		4.0		Very low		
Reconstructive pelvic surgery (including sling surgery for stress urinary incontinence and vaginal prolapse surgery)	Venous thrombo-embolism	Low-risk	1.0	-1.1	Very low	Weak - against	Weak - against
		Medium-risk	3.0	-0.1	Very low	Weak - against	Weak - against
		High-risk	5.0	0.9	Very low	Weak - against	Weak - for
	Bleeding requiring reoperation		3.0		Very low		
Percutaneous nephrolithotomy	Venous thrombo-embolism	Low-risk	2.0	-3.7	Very low	Weak - against	Weak - against
		Medium-risk	4.0	-2.7	Very low	Weak - against	Weak - against
		High-risk	7.0	-1.2	Very low	Weak - against	Weak - for
	Bleeding requiring reoperation		9.0		Low		

* The Panel understands that patients will receive anticoagulation in the peri-operative period. The recommendations against refer to extended prophylaxis.

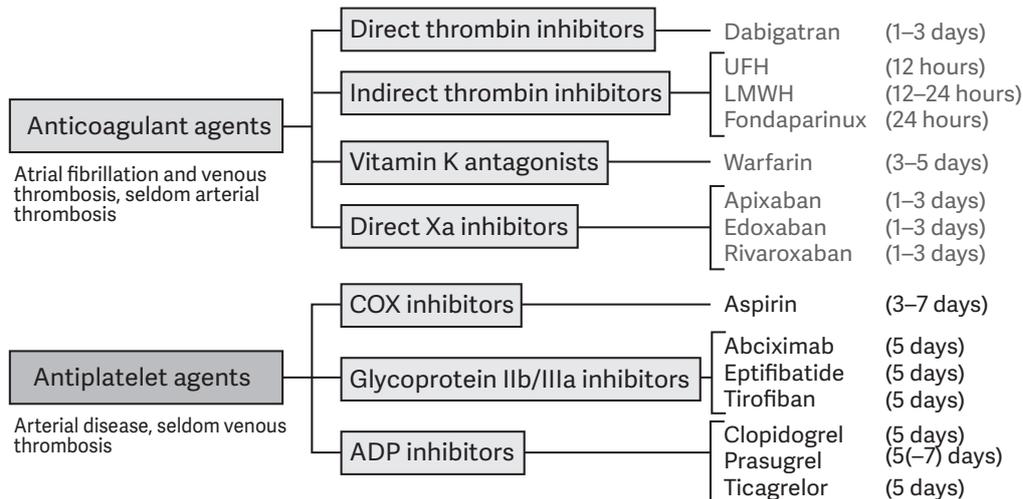
3.2 Peri-operative management of antithrombotic agents in urology

3.2.1 Introduction

In principle, there are four options to manage use of antithrombotic agents (Figure 2) during the peri-operative period: 1) to defer surgery until antithrombotic agents are not needed, 2) stop antithrombotic agents prior to surgery and restart some time after surgery, 3) continue through the surgical procedure, or 4) administer alternative antithrombotic agents that may still reduce the risk of thrombosis but with less risk of bleeding than agents patients are currently using (“bridging”).

Figure 2: The most widely used antithrombotic agents in patients undergoing urologic surgery

Required period of stopping drug before surgery (if desired) provided in parentheses.



3.2.2 Evidence summary

Earlier major guidelines addressing perioperative management of antithrombotic agents in surgery [2, 33–35] preceded recent major studies, including large, rigorous randomised trials [15, 36–38]. With respect to antiplatelet agents, a recent large, rigorous randomised trial comparing aspirin to placebo has demonstrated that aspirin increases post-operative bleeding without reducing arterial thrombotic events [15]. These results provide indirect evidence for antiplatelet agents other than aspirin. Although the absence of large, rigorous placebo-controlled trials to inform recommendations for other antiplatelet agents constitutes a limitation, given similar antithrombotic and bleeding profiles, the indirect evidence provides useful information to inform our recommendations.

Recommendations that preceded the recent much higher-quality evidence often recommended, in the peri-operative context, substitution of alternative agents for the antithrombotic agents patients were using on a regular basis [39]. The recent evidence has demonstrated that bridging increases bleeding without preventing thrombosis. The Panel therefore essentially have two recommendations for patients receiving antithrombotic agents regularly and contemplating surgery: 1) discontinue antithrombotic therapy for the period around surgery, or 2) in those with a temporary very high risk of thrombosis, delay surgery until that risk decreases. If it is not possible to delay, continuing antithrombotic therapy or bridging through surgery may be advisable.

3.2.3 Recommendations

Five days is an appropriate time to stop antiplatelet agents before surgery while the optimal time to stop varies across anticoagulants (for details, see Figure 2).

R24. In all patients receiving antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor), except those with very high risk of thrombosis (see recommendations 26 and 27), the Panel recommends stopping antiplatelet agents before surgery and not initiating any alternative antithrombotic therapy (**strong, high-quality evidence**).

R25. In patients in whom antiplatelet agents have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk – typically four days post-surgery – rather than withholding for longer periods (**strong, moderate-quality evidence**).

R26. In patients with very high risk of thrombosis receiving antiplatelet agents (those with: drug-eluting stent placement within six months; bare metal stent placement within six weeks; transient ischemic attack (TIA) or

stroke within 30 days) in whom surgery can be delayed, the Panel recommends delaying surgery (**strong, high-quality evidence**).

R27. In patients with very high risk of thrombosis receiving antiplatelet agents (those with: drug-eluting stent placement within six months; bare metal stent placement within six weeks; TIA or stroke within 30 days) in whom surgery cannot be delayed, the Panel suggests continuing the drugs through surgery (**weak, low-quality evidence**).

R28. In all patients receiving anticoagulant agents (unfractionated heparin, low molecular weight heparin, warfarin, fondaparinux, dabigatran, apixaban, rivaroxaban, edoxaban), except those with very high risk of thrombosis (see recommendation 26), the Panel recommends stopping drugs before surgery (see Figure 2) and not initiating any alternative antithrombotic therapy (**strong, high-quality evidence**).

Note: Patients with creatinine clearance < 30 ml/min should not receive dabigatran, apixaban, rivaroxaban or edoxaban.

R29. In patients in whom anticoagulants have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk – typically four days post-surgery – rather than withholding for longer periods (**strong, moderate-quality evidence**).

R30. In patients with a new VTE, it is recommended that surgery is delayed for at least one month, and if possible three months, to permit discontinuation of anticoagulation pre-operatively, rather than operating within one month of thrombosis (**strong, high-quality evidence**).

R31. In patients receiving any anticoagulant with a severe thrombophilia, such as antithrombin deficiency and antiphospholipid antibody syndrome, the Panel suggests anticoagulation with either heparin or low molecular weight heparin through surgery, rather than stopping anticoagulation before and after surgery (**weak, low-quality evidence**).

R32. In patients with high-risk mechanical prosthetic heart valves, such as cage-ball valves, receiving warfarin, the Panel recommends bridging with LMWH prior and subsequent to surgery, rather than discontinuing anticoagulation peri-operatively (**strong, high-quality evidence**).

Anticoagulation in these patients involves stopping the warfarin five days prior, commencing LMWH four days prior, omitting LMWH on the day of surgery, and recommencing LMWH and warfarin after surgery.

4. RESEARCH RECOMMENDATIONS

The evidence base for this guideline is limited. Much of the evidence regarding baseline risk is low, or very low quality [8, 9]. Prospective observational studies to establish baseline risk of VTE and bleeding in a wide variety of urologic procedures, as well as addressing patient risk factors for both thrombosis and bleeding, will be necessary to create more definite guidelines. Examples of procedures in which the evidence base is particularly limited include robotic cystectomy, laparoscopic radical nephrectomy, open nephroureterectomy, TURP and prolapse surgery. To confidently establish the baseline risk of VTE and bleeding for specific surgery will require studies that meet certain methodologic standards, such as comprehensive characterisation of the patient populations and follow-up times, documentation of the prophylaxis used, and explicit criteria with demonstration of reproducibility of judgments for documentation of DVT, PE, and bleeding assessments. Furthermore, the optimal timing and duration of thromboprophylaxis remains unclear. Timing and duration questions will be best addressed by large-scale randomised trials.

5. REFERENCES

1. Tikkinen, K.A., *et al.* Systematic reviews of observational studies of risk of thrombosis and bleeding in urological surgery (ROTBUS): introduction and methodology. *Syst Rev*, 2014. 3: 150.
<http://www.ncbi.nlm.nih.gov/pubmed/25540016>
2. Violette, P.D., *et al.* Guideline of guidelines: thromboprophylaxis for urological surgery. *BJU Int*, 2016. 118: 351.
<http://www.ncbi.nlm.nih.gov/pubmed/27037846>
3. Forrest, J.B., *et al.* AUA Best Practice Statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery. *J Urol*, 2009. 181: 1170.
<http://www.ncbi.nlm.nih.gov/pubmed/19152926>
4. Scarpa, R.M., *et al.* Clinically overt venous thromboembolism after urologic cancer surgery: Results from the @RISTOS Study. *Eur Urol*, 2007. 51: 130.
<https://www.ncbi.nlm.nih.gov/pubmed/16942832>
5. Pridgeon, S., *et al.* Venous thromboembolism (VTE) prophylaxis and urological pelvic cancer surgery: a UK national audit. *BJU Int*, 2015. 115: 223.
<http://www.ncbi.nlm.nih.gov/pubmed/25756135>
6. Weinberg, A., *et al.* Nationwide practice patterns for the use of venous thromboembolism prophylaxis among men undergoing radical prostatectomy. *World J Urol*, 2014. 32: 1313.
<http://www.ncbi.nlm.nih.gov/pubmed/24292076>
7. Benyo, M., *et al.* Present practice of thrombosis prophylaxis of radical prostatectomy in a European country: a Hungarian multicenter study. *Urol Int*, 2014. 92: 289.
<http://www.ncbi.nlm.nih.gov/pubmed/24280912>
8. Tikkinen, K.A., *et al.* Procedure-specific risks of thrombosis and bleeding in urological cancer surgery: systematic review and meta-analysis. *Eur Urol*, 2017 (in press).
9. Tikkinen, K.A., *et al.* Procedure-specific risks of thrombosis and bleeding in urological non-cancer surgery: systematic review and meta-analysis. *Eur Urol*, 2017 (in press).
10. Guyatt, G.H., *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 2008. 336: 924.
<http://www.ncbi.nlm.nih.gov/pubmed/18436948>
11. Guyatt, G.H., *et al.* What is "quality of evidence" and why is it important to clinicians? *BMJ*, 2008. 336: 995.
<http://www.ncbi.nlm.nih.gov/pubmed/18456631>
12. Guyatt, G.H., *et al.* Going from evidence to recommendations. *BMJ*, 2008. 336: 1049.
<http://www.ncbi.nlm.nih.gov/pubmed/18467413>
13. Amin, A.N., *et al.* Retrospective administrative database study of the time period of venous thromboembolism risk during and following hospitalization for major orthopedic or abdominal surgery in real-world US patients. *Hosp Pract*, 2011. 39: 7.
<http://www.ncbi.nlm.nih.gov/pubmed/21576893>
14. Sweetland, S., *et al.* Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. *BMJ*, 2009. 339: b4583.
<http://www.ncbi.nlm.nih.gov/pubmed/19959589>

15. Devereaux, P.J., *et al.* Aspirin in patients undergoing noncardiac surgery. *N Engl J Med*, 2014. 370: 1494.
<http://www.ncbi.nlm.nih.gov/pubmed/24679062>
16. Lassen, M.R., *et al.* Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*, 2010. 375: 807.
<https://www.ncbi.nlm.nih.gov/pubmed/20206776>
17. Lassen, M.R., *et al.* Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*, 2010. 363: 2487.
<https://www.ncbi.nlm.nih.gov/pubmed/21175312>
18. Neumann, I., *et al.* Oral direct Factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis. *Ann Intern Med*, 2012. 156:710.
<https://www.ncbi.nlm.nih.gov/pubmed/22412038>
19. Hansson, P.O., *et al.* Deep vein thrombosis and pulmonary embolism in the general population: 'The Study of Men Born in 1913'. *Arch Intern Med*, 1997. 157: 1665.
<http://www.ncbi.nlm.nih.gov/pubmed/9250227>
20. Tosetto, A., *et al.* Prevalence and risk factors of non-fatal venous thromboembolism in the active population of the VITA Project. *J Thromb Haemost*, 2003. 1: 1724.
<http://www.ncbi.nlm.nih.gov/pubmed/12911584>
21. Edmonds, M.J., *et al.* Evidence-based risk factors for postoperative deep vein thrombosis. *ANZ J Surg*, 2004. 74: 1082.
<http://www.ncbi.nlm.nih.gov/pubmed/15574153>
22. Stein, P.D., *et al.* Venous thromboembolism according to age: the impact of an aging population. *Arch Intern Med*, 2004. 164: 2260.
<http://www.ncbi.nlm.nih.gov/pubmed/15534164>
23. Weill-Engerer, S., *et al.* Risk factors for deep vein thrombosis in inpatients aged 65 and older: a case-control multicenter study. *J Am Geriatr Soc*, 2004. 52: 1299.
<http://www.ncbi.nlm.nih.gov/pubmed/15271117>
24. Caprini, J.A. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon*, 2005. 51: 70.
<http://www.ncbi.nlm.nih.gov/pubmed/15900257>
25. Rogers, S.O. Jr., *et al.* Multivariable predictors of postoperative venous thromboembolic events after general and vascular surgery: results from the patient safety in surgery study. *J Am Coll Surg*, 2007. 204: 1211.
<http://www.ncbi.nlm.nih.gov/pubmed/17544079>
26. Parkin, L., *et al.* Body mass index, surgery, and risk of venous thromboembolism in middle-aged women: a cohort study. *Circulation*, 2012. 125: 1897.
<http://www.ncbi.nlm.nih.gov/pubmed/22394567>
27. Pannucci, C.J., *et al.* A validated risk model to predict 90-day VTE events in postsurgical patients. *Chest*, 2014. 145: 567.
<http://www.ncbi.nlm.nih.gov/pubmed/24091567>
28. Gould, M.K., *et al.* Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 2012. 141: e227S.
<http://www.ncbi.nlm.nih.gov/pubmed/22315263>
29. MacLean, S., *et al.* Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 2012. 141: e1S.
<http://www.ncbi.nlm.nih.gov/pubmed/22315262>
30. Bates, S.M., *et al.* Women's values and preferences and health state valuations for thromboprophylaxis during pregnancy: A cross-sectional interview study. *Thromb Res*, 2016. 140: 22.
<https://www.ncbi.nlm.nih.gov/pubmed/27500301>
31. Craigie, S., *et al.* Adherence to mechanical thromboprophylaxis after surgery: a systematic review and meta-analysis. *Thromb Res*, 2015. 136: 723.
<http://www.ncbi.nlm.nih.gov/pubmed/26140737>
32. Guyatt, G.H., *et al.* Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *J Clin Epidemiol*, 2016. 80: 3.
<https://www.ncbi.nlm.nih.gov/pubmed/27452192>

33. Douketis, J.D., *et al.* Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, 2012. 141: e326S.
<http://www.ncbi.nlm.nih.gov/pubmed/22315266>
34. National Clinical Guideline Centre – Acute and chronic conditions (UK). Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. London: Royal College of Physicians (UK); 2010.
35. Culkin D.J., *et al.* Anticoagulation and antiplatelet therapy in urological practice: ICUD/AUA review paper. *J Urol*, 2014. 192: 1026.
<https://www.ncbi.nlm.nih.gov/pubmed/24859439>
36. Douketis, J.D., *et al.* Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*, 2015. 373: 823.
<http://www.ncbi.nlm.nih.gov/pubmed/26095867>
37. Steinberg, B.A., *et al.* Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation*, 2015. 131: 488.
<http://www.ncbi.nlm.nih.gov/pubmed/25499873>
38. Douketis, J.D., *et al.* Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. *Thromb Haemost*, 2015. 113:625.
<https://www.ncbi.nlm.nih.gov/pubmed/25472710>
39. Rose, A.J., *et al.* A call to reduce the use of bridging anticoagulation. *Circ Cardiovasc Qual Outcomes*, 2016. 9: 64. 2016. 9:64.
<https://www.ncbi.nlm.nih.gov/pubmed/26715651>

6. CONFLICT OF INTEREST

All members of the Thromboprophylaxis working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: <http://www.uroweb.org/guidelines/>. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a nonprofit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

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ABBREVIATIONS 2017 EDITION

3IQ	three incontinence questions questionnaire
5-ARIs	5-alpha-reductase inhibitors
5-FU	5-fluorouracil
5-HT	5-hydroxytryptamine
AA	abiraterone acetate
AAST	American Association for the Surgery of Trauma
ABP	antibiotic prophylaxis
ABP	acute bacterial prostatitis
ABS-GEC-ESTRO	American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology
ABSST	Actionable Bladder Symptom Screening Tool
ABU	asymptomatic bacteriuria
AC	adenocarcinoma
ACD-RCC	acquired cystic disease-associated RCC
ACE	angiotensin-converting enzyme
ACKD	acquired cystic kidney disease
ACT	adjustable compression therapy (device)
ACTH	adrenocorticotrophic hormone
AD	autonomic dysreflexia
ADL	activities of daily living
ADPKD	adult dominant polycystic disease
ADT	androgen-deprivation therapy
AFP	alpha-fetoprotein
AGS	adrenogenital syndrome
AHRQ	Agency for Healthcare Research and Quality
AIPE	Arabic Index of Premature Ejaculation
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALPP	abdominal leak point pressure
AMH	anti-Müllerian hormone
AML	angiomyolipoma
AMPA	amino-methylene-phosphonic acid
APCKD	adult polycystic kidney disease
AR	androgen receptor
ARF	acute renal failure
ARM	anorectal malformation
ART	assisted reproduction technique
ART	adjuvant radiotherapy
AS	active surveillance
ASA	American Society of Anesthesiologists
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiology and Oncology
ATP	adenosinetriphosphate
AUA	American Urological Association
AUC	area under curve
AUR	acute urinary retention
AUS	artif al urinary sphincter
AVF	arteriovenous fistulae
AVP	arginine vasopressin
BBD	bladder and bowel dysfunction
BC	bladder cancer
BCF	biochemical failure
BCG	bacillus Calmette-Guérin
BCR	biochemical recurrence
BDFS	biochemical disease-free survival
BDNF	brain-derived neurotrophic factor
BEP	cisplatin, etoposide, bleomycin
BLI	β -lactamase inhibitor

BMD	Bone mineral density
BMG	buccal mucosa grafts
BMI	body mass index
BMP	cisplatin, methotrexate and bleomycin
bNED	biochemically no evidence of disease
BOO(I)	bladder outlet obstruction (index)
BPE	benign prostatic enlargement
BPH	benign prostatic hyperplasia
BPO	benign prostatic obstruction
BPS	bladder pain syndrome
B-SAQ	bladder self-assessment questionnaire
BS	bone scan
BSC	best supportive care
BSW	benefit, satisfaction with treatment and willingness
BT	bladder training
BT	brachytherapy
BTA	bladder tumour antigen
BTX	botulinum toxin
BTX-A	Botulinum toxin A
BUN	blood urea nitrogen
BVM	bleomycin-vincristine-methotrexate
BWT	bladder wall thickness
BXO	balanitis xerotica obliterans
CAB	complete (or maximal or total) androgen blockade
CAD	coronary artery disease
CAD	complete androgen deprivation
CAG	cytosine-adenine-guanine
CAH	congenital adrenal hyperplasia
CaX	carbonic anhydrase
CaPSURE	Cancer of the Prostate Strategic Urologic Research Endeavour
CAUTIs	catheter-associated urinary tract infections
CBAVD	congenital bilateral absence of the vas deferens
CBT	cognitive behavioural therapy
CCF	Cleveland Clinic Foundation
CCH	clostridium collagenase
CCI	Charlson Comorbidity Index
CF	chronic fatigue
CF	cystic fibrosis
CFS	chronic fatigue syndrome
CFU	colony forming unit
CFTR	cystic fibrosis transmembrane conductance regulator
Cg A	chromogranine A
CGA	comprehensive geriatric assessment
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHF	congestive heart failure
chRCC	chromophobe renal cell cancer
CI	confidence interval
CIC	clean intermittent catheterisation
CIRS	cumulative illness rating scale
CIS	carcinoma in situ
CISCA	cisplatin, cyclophosphamide, and adriamycin
CISR-G	cumulative illness score rating-geriatrics
CKD	chronic kidney disease
CLSS	core lower urinary tract symptom score
CM	cisplatin, methotrexate
Cmax	maximal concentration
CMV	cytomegalovirus
CN	cytoreductive nephrectomy
CNS	central nervous system

COLD	cryo on-line data
Contlife®	quality of life assessment questionnaire concerning urinary incontinence
CombAT	combination of Avodart® and Tamsulosin
COPUM	congenital obstructive posterior urethral membrane
CPA	cyproterone acetate
CPP	chronic pelvic pain
CPPS	chronic pelvic pain syndrome
cPSA	complex PSA
CPSI	chronic prostatitis symptom index
CR	complete response
cRCC	clear cell renal cell cancer
CrCl	calculation of creatinine clearance
CRH	corticotrophin-releasing hormone
CRP	C-reactive protein
CRPC	castration-resistant prostate cancer
CRS	caudal regression syndrome
CRT	conformal radiotherapy
CS	clinical stage
CSAP	cryosurgical ablation of the prostate
CSS	cancer-specific survival
CT	computed tomography
CTC	circulating tumour cells
CTC AE	Common Terminology criteria for Adverse Events
CTU	computed tomography urography
CUETO	Club Urológico Español de Tratamiento Oncológico (Spanish Oncology Group)
CVA	cerebrovascular
CVD	cardiovascular disease
CyA	Cyclosporin A
DAN-PSS	Danish prostate symptom score
DARE	database of abstracts of reviews of effectiveness
DCE	dynamic contract enhanced
DDAVP	desmopressin
DES	diethylstilbestrol
DFS	disease-free survival
DHT	dihydrotestosterone
DHTST	dihydrotestosterone
DICC	dynamic infusion cavernosometry or cavernosography
DLPP	detrusor leak point pressure
DMSA	dimercaptosuccinic acid
DMSO	dimethyl sulphoxide
DNIC	diffuse noxious inhibitory control
DO	detrusor overactivity
DRE	digital rectal examination
DRG	dorsal root ganglion
DSD	disorders of sex development
DSD	detrusor sphincter dyssynergia
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision
DSNB	dynamic sentinel node biopsy
DSS	disease-specific survival
DT	doubling time
DTPA	diethylenetriamine pentaacetate
DWI	diffusion-weighted imaging
DWT	detrusor wall thickness
EAA	European Academy of Andrology
EAU	European Association of Urology
EBL	estimated blood losses
EBM	evidence-based medicine
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
ED	erectile dysfunction

EEC	extracapsular extension of carcinoma
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
EH	excisional haemorrhoidectomy
EHL	electrohydraulic lithotripsy
eLND	extended lymph node dissection
EMA	European Medicines Agency
EMDA	transdermal electromotive drug administration or electromotive drug administration
EMEA	European Medicines Agency
EMG	electromyography
eNOS	endothelial NOS
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-GUCG	European Organisation for Research and Treatment of Cancer - Genito-Urinary Cancer Group
EP	etoposide, cisplatin
EPC	Early Prostate Cancer Trialists' Group
EPIQ	epidemiology of prolapse and incontinence questionnaire
EPS	expressed prostatic secretion
ePTFE	expanded polytetrafluoroethylene
EQ	euro quality
ER	extended release
ERSPC	European Randomized Screening for Prostate Cancer
ES	electrical stimulation
ESR	erythrocyte sedimentation rate
ESSIC	International Society for the Study of BPS
ESTRO	European Society for Radiotherapy & Oncology
ESWT	extracorporeal shock wave treatment
EUCAST	European Committee for Antimicrobial Susceptibility Testing
FACT	functional assessment of cancer therapy
FACT-P	functional assessment of cancer therapy-prostate
FAP	familial amyloidotic polyneuropathy
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose-positron emission tomography
FISH	fluorescent in situ hybridisation
FIT	functional incidental training
FM	fibromyalgia
FNA	fine-needle aspiration
FNAB	fine-needle aspiration biopsy
FNAC	fine needle aspiration cytology
FS2S	first stage of two-stage (implantation of sacral neuromodulator)
FSFI	female sexual function index
FSH	follicle stimulating hormone
FSRT	fractionated stereotactic radiotherapy
FSSs	functional somatic syndromes
FVC	frequency volume chart
G6PD	glucose-6-phosphate dehydrogenase
GABA	gamma-aminobutyric acid
GAG	glycosaminoglycan
GAQ	general assessment question
GC	gemcitabine, cisplatin
G-CSF	granulocyte colony stimulating factor
GCT	germ cell tumour
GETUG	Groupe d'Etude des Tumeurs Uro-Génitales
GFR	glomerular filtration rate
GHQ	general health questionnaire
GI	gastrointestinal
GITS	gastrointestinal therapeutic system
GnRH	gonadotropin-releasing hormone
GR	grade of recommendation

GREAT	G-protein-coupled receptor affecting testis descent
GS	gleason score
GSSAB	Global Study of Sexual Attitudes and Behaviors
GU	genitourinary
GWAS	genome-wide association studies
HAD scale	hospital anxiety and depression scale
HAL	hexaminolaevulinic acid
HBO	Hyperbaric oxygen
hCG	human chorionic gonadotropin
HD-MVAC	high-dose intensity MVAC
HDR	high-dose rate
HGPIN	high grade prostatic intraepithelial neoplasia
HIF	hypoxia inducible factor
HIFU	high-intensity focused ultrasound
HIV	human immunodeficiency virus
HLRCC	hereditary leiomyomatosis and renal cell cancer
HMG	human menopausal gonadotropin
HNPCC	hereditary non-polyposis colorectal carcinoma
Ho:YAG	holmium:yttrium-aluminium-garnet (laser)
HoLEP	holmium laser enucleation
HoLRP	holmium laser resection of the prostate
HOPE	hypospadias objective penile evaluation
HOSE	hypospadias objective scoring evaluation
HP	hyperprolactinemia
HPF	high-power field
HPLC	high-performance liquid chromatography
HPT	hyperparathyroidism
HPV	human papillomavirus
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
HRQoL	health-related quality of life
HT	hormonal therapy
HTA	health technology appraisal
HUI	health utilities index
IAD	intermittent androgen deprivation
IARC	International Agency for Research on Cancer
IASP	Association for the Study of Pain
IBS	irritable bowel syndrome
IBT	iatrogenic bladder trauma
IC	intermittent catheterisation
ICCS	International Children's Continence Society
ICD-10	International Classification of Diseases-10
ICDB	Interstitial Cystitis Data Base
ICIQ	international consultation on incontinence modular questionnaire
ICIQ-FLUTS	ICIQ-female lower urinary tract symptoms
ICIQ-MLUTS	ICIQ-male lower urinary tract symptoms
ICIQ-VS	International Consultation on Incontinence Questionnaire – Vaginal Symptoms
ICS	International Continence Society
ICSI	interstitial cystitis symptom index
ICSI	intracytoplasmic sperm injection
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IED	improvised explosive device
IELT	intravaginal ejaculatory latency time
IF	impact factor
IFIS	intra-operative floppy iris syndrome
IGCCCG	International Germ Cell Cancer Collaborative Group
IGCNU	intratubular germ cell neoplasia, unclassified type
IGRT	image-guided radiotherapy
IHH	isolated (formerly termed idiopathic) hypogonadotrophic hypogonadism

IIEF	international index of erectile function
IIQ	incontinence impact questionnaire
IKCWG	International Kidney Cancer Working Group
IL	interleukin
IL-6	interleukin-6
IMDC	International Metastatic Renal Cancer Database Consortium
IMRT	intensity modulated radiotherapy
INR	international normalised ratio
IOQ	incontinence outcome questionnaire
IPCN	International Prostatitis Collaborative Network
IPD	idiopathic parkinson's disease
IPE	index of premature ejaculation
IPP	intravesical prostatic protrusion
IPSS	international prostate symptom score
I-QOL	incontinence quality of life
I-QOL (ICIQ-Uqol)	urinary incontinence-specific quality of life instrument
IR	immediate release
IRS	infrared spectroscopy
IRT	iarogenic renal trauma
ISI	incontinence severity index
ISQ	incontinence stress index
ISS	incontinence symptom severity index
ISSM	International Society for Sexual Medicine
ISSVD	Society for the Study of Vulvovaginal Disease
ISUP	International Society of Urological Pathology
ITGCN	intratubular germ cell neoplasia
ITGCNU	intratubular germ cell neoplasia of unclassified type
ITT	intent-to-treat
IU	international unit
IUGA	International Urogynecological Association
IUSS	indevus urgency severity
IVC	inferior vena cava
IVF	in vitro fertilisation
IVP	intravenous pyelogram
IVU	intravenous urography
JESS	joint expert speciation system
KHQ	king's health questionnaire
KUB	kidney ureter bladder
LAD	lymphadenectomy
LARP	laparoscopic radical prostatectomy
LDH	lactate dehydrogenase
LDR	low-dose rate
LE	level of evidence
LESS	laparoendoscopic single-site
LET	linear energy transfer
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LI-SWT	low-intensity extracorporeal shock wave therapy
LIS	Leicester impact scale
LMNL	lower motor neuron lesion
LN	lymph node
LND	lymph node dissection
LN _s	lymph nodes
LPN	laparoscopic partial nephrectomy
LPP	leak point pressure
LPP	laparoscopic pyeloplasty
LRN	laparoscopic radical nephrectomy
LRP	laparoscopic radical prostatectomy
LUSQ	Leicester urinary symptom questionnaire
LUT	lower urinary tract

LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
LUTS Tool	lower urinary tract symptoms tool
LVD	left ventricular dysfunction
MAB	maximal androgen blockade
MACE	major cardiovascular events
MAG-3	mercaptoacetylglycine
MAGI	male accessory gland infection
MAPP	Multi-disciplinary Approach to the study of chronic Pelvic Pain research
MAR	mixed antiglobulin reaction
MASRI	medication adherence self-report inventory
MBD	metastatic bone disease
M-CAVI	compared methotrexate/carboplatin/vinblastine
MESA	microsurgical epididymal sperm aspiration
MESA-Q	medial epidemiological and social aspects of aging questionnaire
MeSH	medical subject headings
MET	metabolic equivalent system
MET	medical expulsive therapy
MFS	metastasis-free survival
MFSR	metastasis-free survival rate
MI	myocardial infarction
MIBC	muscle-invasive bladder cancer
mILND	modified inguinal lymphadenectomy
MMAS	Massachusetts Male Aging Study
MMC	mitomycin
MMC	myelomeningocele
MPA	medroxyprogesterone acetate
mpMRI	multiparametric magnetic resonance imaging
MPR	medication possession rate (drug adherence)
MRA	MRI biphasic angiography
MRC	Medical Research Council
MRI	magnetic resonance imaging
MRSA	methicillin-resistant Staphylococcus aureus
MRU	magnetic resonance urography
MS	multiple sclerosis
MSA	multiple sytem atrophy
MSAM	multinational survey on the aging male
MSHQ-EJD	male sexual health questionnaire ejaculatory dysfunction
MSI	microsatellite instability
MSKCC	Memorial Sloan-Kettering Cancer Centre classification
MSU	mid-stream sample of urine
MTOPS	medical therapy of prostatic symptoms
MTS	cell proliferation assay
MUI	mixed urinary incontinence
MVA	methotrexate, vinblastine, adriamycin
MVAC	methotrexate, vinblastine, adriamycine and cisplatin
NAION	non-arteritic anterior ischemic optic neuropathy
NBSs	non-bladder syndromes
NC	nephrocalcinosis
NCCLS	National Committee for Clinical Laboratory Standards
NCCN	National Comprehensive Cancer Network
NCCT	non-contrast enhanced computed tomography
NCIC	National Cancer Institute of Canada
NCT-CTC	National Cancer Institute Common Toxicity Criteria
Nd:YAG	neodymium:yttrium-aluminum-garnet
NDO	neurogenic detrusor overactivity
NDSD	neurogenic detrusor-sphincter dysfunction
NGF	nerve growth factor
NHSLs	National Health and Social Life Survey
NHT	neoadjuvant hormonal therapy

NICE	National Institute for Health and Clinical Excellence
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NIH-CPSI	NIH Prostatitis Symptom Index
NLUTD	neurogenic lower urinary tract dysfunction
NMDA	N-methyl-D-aspartate
NMIBC	non-muscle-invasive bladder cancer
nNOS	neuronal
NNT	number needed to treat
NO	nitric oxide
NOA	non-obstructive azoospermia
NOS	NO synthases
NPTR	nocturnal penile tumescence and rigidity
NPV	negative predictive value
N-QoL	nocturia quality of life questionnaires
NRS	non-randomized studies
NS	nerve sparing
NSAA	non-steroidal anti-androgen
NSAIDs	non-steroidal anti-inflammatory drugs
NSF	nephrogenic systemic fibrosis
NSGCT	non-seminomatous germ cell tumour
NSQIP	national surgical quality improvement programme
NSRP	nerve-sparing radical prostatectomy
NVB	neurovascular bundle
NYHA	New York Heart Association
O/E	ratio of observed versus expected
OA	obstructive azoospermia
OAB	overactive bladder
OAB-q (ICIQ-OABqol)	overactive bladder questionnaire
OAB-S	overactive bladder satisfaction measure
OAB-SAT-q	OAB satisfaction questionnaire
OAB-SS	overactive bladder symptom score
OAB-v3	OAB short form
OAB-v8	OAB awareness tool
OAT	oligo-astheno-teratozoospermia [syndrome]
OCAS	oral controlled absorption system
ORC	open radical cystectomy
ORP	open retropubic radical prostatectomy
ORR	overall response rate
OS	overall survival
OSA	obstructive sleep apnoea
PA	para-aortic
PADUA	preoperative aspects and dimensions used for an anatomical
PAG	periaqueductal grey
PCa	prostate cancer
PCN	percutaneous nephrostomy
PCNL	percutaneous nephrolithotomy
PCOS	prostate cancer outcomes study
PCP	pneumocystis carinii pneumonia
PCPT	prostate cancer prevention trial
PCPTRC	prostate cancer prevention trial risk calculator
pCR	pathologically complete remissions
PCR	pathological complete remission
PCSM	prostate-cancer-specific mortality
PCWG	prostate cancer working group
PD	Peyronie's disease
PD	Parkinson's disease
PD-1L	programmed death-1 ligand
PDD	photodynamic diagnosis
PDE5i	phosphodiesterase type 5 inhibitors

PDGF	platelet-derived growth factor
PDQ	Peyronie's disease-specific questionnaire
PE	premature ejaculation
PEDT	premature ejaculation diagnostic tool
PEI	cisplatin, etoposide, ifosfamide
PEP	premature ejaculation profile
PEPA	premature ejaculation prevalence and attitudes
PESA	percutaneous epididymal sperm aspiration
PET	positron emission tomography
PET/CT	positron emission tomography, computed tomography
PFBQ	pelvic floor bother questionnaire PFDI
(PFDI-20)	pelvic floor distress inventory (short form)
PFIQ (PFIQ-7)	pelvic floor impact questionnaire (short form)
PFMT	pelvic floor muscle training
PFS	pressure flow study
PFS	progression-free survival
PGD	preimplantation genetic diagnosis
PGI-I and PGI-S	patient global impression of severity and improvement
PH	primary hyperoxaluria
PHI	prostate health index
PICO	population, intervention, comparison, outcome
PID	pelvic inflammatory disease
PIN	prostatic intraepithelial neoplasia
PIRADS	prostate imaging reporting and data system
PISQ	pelvic organ prolapse/urinary incontinence sexual questionnaire
PIVOT	prostate cancer intervention versus observation trial
PLAP	placental alkaline phosphatase
PLCO	prostate, lung, colorectal and ovary
PLND	pelvic lymph node dissection
PMB	prostate mapping biopsy
PMSES	broome pelvic muscle exercise self- efficacy scale
PN	partial nephrectomy
PNE	percutaneous nerve evaluation
PNH	perinephritic hematoma
PNL	percutaneous litholapaxy
PNL	percutaneous nephrolithotomy
PNS	pudendal nerve stimulation
POP	pelvic organ prolapse
POSEI	postoperative stress urinary incontinence
POSQ	primary OAB symptom questionnaire
PPBC	patient perception of bladder condition
PPI	post-prostatectomy urinary incontinence
PPIUS	patient's perception of intensity of urgency scale
PPMT	pre-post-massage test
PPQ	patient preparation questionnaire
PPS	prostate pain syndrome
P-PTNS	percutaneous posterior tibial nerve stimulation
PPV	positive predictive value
pRCC	papillar renal cell cancer
PRAFAB	protection, amount, frequency, adjustment, body image)
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PRO	patient reported outcome
PROMS	patient reported outcome measures
PS	performance status
PS	pathological stage
PSA	prostate specific antigen
PSADT	PSA doubling time
PSAV	PSA velocity
PSM	positive surgical margin
PTEN	phosphatase and tensin homolog

PTH	parathyroid hormone
PTNS	posterior tibial nerve stimulation
PTNS	percutaneous tibial nerve stimulation
PTT	partial thrombolastin time
PUNLMP	papillary urothelial neoplasms of low malignant potential
PUF	patient symptom scale (pelvic pain, urgency and frequency)
PUV	posterior urethral valves
PVB	cisplatin, vinblastine, bleomycin
PVR	post void residual
PWS	Prader-Willi syndrome
QALY	quality-adjusted life year
Qave	average urinary flow rate
Qmax	maximum urinary flow rate
Qol	quality of life
QUALYs	quality-of-life-adjusted gain in life years
QUID	questionnaire for urinary incontinence diagnosis
RALC	robotic-assisted laparoscopic cystectomy
RALP	robotic-assisted laparoscopic prostatectomy
RALRP	robotic-assisted laparoscopic radical prostatectomy
RALS	robot-assisted laparoscopic sacrocolpopexy
RANKL	receptor activator of nuclear factor KB ligand
RARC	robot-assisted radical cystectomy
RARP	robot-assisted radical prostatectomy
RAT	renal angiomyomatous tumour
RBL	rubber band ligation
RC	radical cystectomy
RCC	renal cell cancer
RCT	randomised controlled trial
RECIST	response evaluation criteria in solid tumours
REMS	risk evaluation and mitigation strategy
REST	renal epithelial and stromal tumours
RFA	radiofrequency ablation
RFS	recurrence-free survival
RIRS	retrograde renal surgery
RLPP	robot-assisted laparoscopic pyeloplasty
RN	reflux nephropathy
RN	radical nephrectomy
RNC	radionuclide cystography
RNU	radical nephroureterectomy
RP	radical prostatectomy
RPA	recursive partitioning analysis
RPLND	retroperitoneal lymph node dissection
RPN	robotic partial nephrectomy
RR	recurrent stones
RR	relative risk
RRN	robotic radical nephrectomy
RRP	radical retropubic prostatectomy
RT	radiotherapy
RTA	renal tubular acidosis
RTOG	Radiation Therapy Oncology Group
RTX	resiniferatoxin
SAE	selective arterial embolization
SAGA	self-assessment goal achievement questionnaire
SARS	sacral anterior root stimulation
SAT	severe acute toxicity
SB	spina bifida
SBRT	stereotactic body radiotherapy
SCC	squamous cell carcinoma
SCI	spinal cord injury
SDH	succinate dehydrogenase

SEER	surveillance, epidemiology and end results
SELECT	selenium and vitamin E cancer prevention trial
SEP	sexual encounter profile
SF	short form
SFR	stone free rate
SGA	standardized geriatric assessment
SHBG	sex hormone binding globulin
SHIM	sexual health inventory for men
SIGN	Scottish Intercollegiate Guideline Network
SIOG	International Society of Geriatric Oncology
SIRS	systemic inflammatory response syndrome
SIS	small intestinal submucosa
SITUS	single-incision triangulated umbilical surgery
SMX	sulphamethoxazole
SNB	sentinel node biopsy
SNM	sacral neuromodulation
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4
SQoL-F	sexual quality of life - female
SR	systematic review
SR	sustained release
SRE	skeletal-related events
SRS	stereotactic radiosurgery
SRT	salvage radiotherapy
SRY	sex region of the Y chromosome
SSI	surgical site infection
SSI and SII	symptom severity index and symptom impact index for stress incontinence in women
SSRI	selective serotonin reuptake inhibitor
SSRIs	selective serotonin reuptake inhibitors
STD	sexually transmitted disease
SUI	stress urinary incontinence
SUIQ	stress/urge incontinence questionnaire
SV	seminal vesicle
SVI	seminal vesicle invasion
SWENOTECA	Swedish-Norwegian Testicular Cancer Project
SWL	shock wave lithotripsy
SWOG	Southwest Oncology Group
$t_{1/2}$	elimination half-life
TBS	treatment benefit scale
TBT-O	transobturator tension-free vaginal tape
TC	testicular cancer
TC99m	technetium 99m
TCC	transitional cell carcinoma
Tc-MAG3 (99m)	technetium-99m mercaptoacetyltriglycine (MAG3)
TCS	testicular cancer survivor
TDS	testicular dysgenesis syndrome
TDS	transdermal delivery system
TEFNA	testicular fine-needle aspiration
TEMPE	topical eutectic mixture for premature ejaculation
TENS	transcutaneous electrical nerve stimulation
TESE	testicular sperm extraction
TGCT	testicular germ cell tumour
TGF 1	transforming growth factor [®] 1
ThuLEP	tm:YAG laser enucleation of the prostate
ThuVaP	tm:YAG vaporization of the prostate
ThuVaRP	tm:YAGvaporesection
ThuVEP	tm:YAGvapoenucleation
TIN	testicular intraepithelial neoplasia
TIP	paclitaxel, cisplatin, and ifosfamide
TIP	tubularised incised plate urethroplasty
TIP	paclitaxel, ifosfamide, cisplatin

TK	tyrosine kinase
TKI	tyrosine kinase inhibitors
TM	testicular microlithiasis
Tmax	time to maximum plasma concentration
TMP	trimethoprim
TNF	tumour necrosis factor
TNM	tumour, node, metastasis (classification)
TPA	tissue plasminogen activator
T-PTNS	transcutaneous posterior tibial nerve stimulation
TRCC	MiT translocation renal cell carcinomas
TROG	Trans-Tasman Oncology Group
TRT	testosterone replacement therapy
TRUS	transrectal ultrasound
TS	tuberous sclerosis
TST	testosterone
TT	tumour thrombus
TTP	time to progression
TUNA	transurethral needle ablation
TUR	transurethral resection
TURB	transurethral resection of the bladder
TURED	transurethral resection of the ejaculatory ducts
TURP	transurethral resection of the prostate
TVT	tension-free vaginal tape
TVTS	tension-free vaginal tape secure
TWOC	trial without catheter
UAB	underactive bladder
UC	urothelial carcinomas
UCB	urothelial carcinoma of the bladder
UDI (UDI-6)	urogenital distress inventory (-6)
UDS	urodynamic study
UEBW	ultrasound-estimated bladder weight
U-IIQ	urge incontinence impact questionnaire
UI	urinary incontinence
UI-4	urinary incontinence -4 questionnaire
UICC	Union for International Cancer Control
UIHI	urinary incontinence handicap inventory
UIQ	urinary incontinence questionnaire
UISS	urinary incontinence severity score
ULN	upper limit of normal
UMNL	upper motor neuron lesion
UPJ	ureteropelvic junction
UPScale	urgency perception scale
UPScore	urgency perception score
UQ	urgency questionnaire
URR	urethral reflectometry
URS	ureterorenoscopy
US	ultrasound
US PSA	ultra-sensitive PSA
USIQ-QOL	urgency severity & intensity questionnaire: symptom severity
USIQ-S	urgency severity & intensity questionnaire: quality of life
USP	urinary symptom profile
USPIOs	ultra-small particles of iron oxide
USS	urinary sensation scale
UTI	urinary tract infection
UTIs	urinary tract infections
UTUC	upper tract urothelial carcinoma
UUI	urgency urinary incontinence
UUT	upper urinary tract
uUTI	uncomplicated urinary tract infection
UVJ	ureterovesical junction

VA	US Veterans Administration
VACURG	Veterans Administration Co-operative Urological Research Group
VAPS	visual analogue pain scale
VAS	visual analogue scale
VB1	first-voided urine
VB2	mid-stream urine
VB3	voided bladder urine-3
VBM	vinblastine, bleomycin, methotrexate
VC	vena cava
VCD	vacuum constriction devices
VCU	voiding cystourethrography
VCUG	voiding cystourethrography
VED	vacuum erection devices
VEGF	vascular endothelial growth factor
VelP	vinblastine, ifosfamide, cisplatin
VHL	Von Hippel-Lindau
VIP	vasoactive intestinal peptide
VIP (VP-16)	etoposide, ifosfamide, cisplatin
VR	vesicorenal reflux
VTT	venous tumour thrombus
VUD	video-urodynamic
VUR	vesicoureteric reflux
VUS	voiding urosonography
WBC	white blood cell
WBRT	whole brain radiotherapy
WHO	World Health Organization
WI	weighted imaging
WIT	warm ischaemia time
WW	watchful waiting
XRD	X-ray diffraction
ZA	zoledronic acid

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