European Association of Urology Guidelines

2016 edition

European Association of Urology

Guidelines

2016 edition

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of Urology**

European Association of Urology Guidelines - 2016

Introduction

We are honoured to present the 2016 edition of the European Association of Urology (EAU) Guidelines. Clinical Practice Guidelines are a highly influential tool for the improvement of clinical care, the harmonisation of healthcare provision as well as the management of healthcare associated resources across Europe. Therefore, clinical guidelines must be free of bias, presenting a balanced view of risks and benefits, in which the preferences of patients, best clinical practice and healthcare policy needs are underpinned by the best available scientific evidence.

To achieve these essential attributes, the EAU Guidelines Office has systematically introduced Cochrane review methodology across all 20 Guidelines Panels, ensuring that high quality systematic reviews underpin key recommendations. This process is ongoing and would not be possible without the continued work of our exceptional team of young doctors, actively involved in the EAU Guidelines Office Associates Programme, under the leadership of our expert Panel Members who represent some of the most respected, talented and dedicated urologists from across Europe and beyond. The success of our systematic review policy is measurable in the numerous European Urology publications, for which the EAU Guidelines Office is exceptionally grateful for the support of Prof.Dr. James Catto editor-in-chief of European Urology. Currently there are another 36 ongoing systematic reviews, the results of which will become more apparent in subsequent updates of the Guidelines.

The EAU Guidelines Office is committed to ensuring that the clinical questions on which recommendations are based, and the outcomes of interest that are considered, take important patient views into account. Therefore, whenever possible, valuable input from patient advocacy groups and lay reviewers are sought. It is a key aim of the EAU Guidelines Office to increase structured patient involvement in Guidelines development over the course of successive updates, with the hope of developing a more patient-centred shared-decision making framework.

Development of Clinical Practice Guidelines, whilst important, must fundamentally be supported by an effective dissemination strategy. To enhance the dissemination of the EAU Guidelines recommendations, the Social Media (SoMe) working group chaired by Prof.Dr. Maria Ribal has been tasked with promoting discussion and triggering feedback from guidelines users via Facebook and Twitter. From its official start in January 2015, the hashtag #eauguidelines has disseminated over 3,000 tweets resulting in upwards of three million impressions and leading to a 40% increase in the number of followers of the EAU Twitter account @uroweb. A considerable proportion of the success of the EAU Guidelines can be attributed to the support of the 41 National Urological Societies worldwide who actively endorse the EAU Guidelines. National Society endorsement shows support of the EAU Guidelines as a reference standard complementary to their own National Guidelines whilst also driving dissemination of the EAU Guidelines amongst all practicing urologists within each individual society.

Effective dissemination of the EAU Guidelines, whilst important, must be followed-up by assessment of their impact on clinical practice. In order to achieve this, the EAU Guidelines Office has launched the IMpact Assessment of Guidelines Implementation and Education (IMAGINE) group, chaired by Prof.Dr. Alberto Briganti. It is the firm belief of the IMAGINE group that evidence-based medicine should be complemented by evidence-based implementation. It is the goal of the group to establish a knowledge translation setting which will allow the gap between evidence and practice to be bridged. Key to this endeavour, in conjunction with effective dissemination and education, is the identification of barriers to knowledge transfer, or more importantly, the identification of the optimum interventions to limit or overcome such barriers; ultimately, making the EAU Guidelines recommendations more relevant and actionable whilst enhancing their influence on patient care.

The yearly publication of the EAU Guidelines would not be possible without the unwavering support of every user of the Guidelines globally, our EAU membership, our highly valued Guidelines Panels, the young Guidelines Associates, the EAU Executive Committee (particularly the constant support of Prof.Dr. Hein van Poppel) and Management team, and our National Societies. So, on behalf of the EAU Guidelines Office Board, thank you for your support and inspiration. We hope you enjoy using the 2016 update of the EAU Guidelines!

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Methodology section

Clinical guidelines development is one of the core activities of the EAU, with the 2016 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 250 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 sustained quality improvement;
• contribute to the dissemination and implementation of all EAU Guidelines publications.

All EAU Guidelines can be accessed online through the Association website: www.uroweb.org/guidelines/. All full members of the EAU can collect print copies of both the full text guidelines and a short reference document (Pocket guidelines) free of charge at EAU annual meetings. A mobile App containing the Pocket guidelines is also available for download.

Systematic Review development
The EAU GO has 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 Guidelines 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.

In the course of 2015, 43 SRs were initiated. 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 the outcomes are reported homogenously. 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 system
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].

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5. Moher, D., *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol, 2009. 62: 1006.
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The Assistance and support of National Urological Associations has been invaluable for the EAU guidelines project over the past number of 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 Argentinian Society of Urology
The Armenian Association of Urology
The Austrian Urological Society
Urological Society of Australia and New Zealand
The Belarusian Association of Urology
Belgische Vereniging voor Urologie
Société Belge d'Urologie
The British Association of Urological Surgeons
La Sociedad Chilena de Urología
The Chinese Urological Association
La Sociedad Colombiana de Urología
The Cyprus Urological Association
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Association Française d'Urologie
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The Hellenic Urological Association
The Hong Kong Urological Association

The Hungarian Urological Association
The Indonesian Urological Association
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The Italian Association of Urology
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The Polish Urological Association
The Portuguese Urological Association
The Russian Society of Urology
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EAU Guidelines on

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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) Ta, T1 and CIS. The information presented is limited to urothelial carcinoma, unless specified otherwise. The aim is to provide practical guidance on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

Separate EAU guidelines documents are available addressing upper tract urothelial carcinomas (UTUCs) [1], muscle-invasive and metastatic bladder cancer (MIBC) [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.

1.2 Panel composition

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including 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 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, as are a number of translations of all versions of the EAU NMIBC Guidelines. All documents can be accessed on the EAU website.

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 2016 NMIBC guidelines document presents a limited update of the 2015 full text document.

1.4.2 Summary of changes

Key changes in this 2016 print:

1.4.2.1 Changes in recommendation

- In Section 5.16 – a recommendation has been added:

Recommendations for TURB and/or biopsies, tumour classification and pathology report	GR
In patients suspected of harbouring bladder cancer TURB followed by pathology investigation of the obtained specimen(s) is recommended as a diagnostic procedure and initial treatment step.	A

TURB = transurethral resection of the bladder.

- Section 7.2.1.1 - A single, immediate, post-operative intravesical instillation of chemotherapy – has been expanded to include the findings of 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? [4].

- The recommendations as presented in Section 7.5 and Table 7.6 - Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification - have been adapted. The recommendation grade did not change.

Section 7.5 Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS	GR
In patients with tumours presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate chemotherapy instillation is recommended.	A

CIS = carcinoma in situ; EORTC = European Organization for Research and Treatment of Cancer.

Table 7.6 - Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification

Risk category	Definition	Treatment recommendation
Intermediate-risk tumours	All cases between categories 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 1-year full-dose BCG treatment (induction plus 3-weekly instillations at 3,6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 year.

BCG = Bacillus Calmette-Guérin; EORTC = European Organization for Research and Treatment of Cancer; TURB = transurethral resection of the bladder.

1.4.2.2   Summary of evidence
- Section 3.4 - A summary of evidence has been added to Chapter 3 – Epidemiology, aetiology and pathology.
- Section 4.7 – A summary of evidence has been added to Chapter 4 – Staging and classification systems.
- Section 5.15 - Summary of evidence has been added to Chapter 5 – Diagnosis.
- Section 6.4 – A summary of evidence has been added to Chapter 6 – Predicting disease recurrence and progression.
- Section 7.2.1.4 – A summary of evidence has been added to Section 7.2.1 Intravesical chemotherapy.
- Section 7.2.2.7 – A summary of evidence has been added to Section 7.2.2 Intravesical bacillus Calmette Guérin immunotherapy.
- Section 7.2.4.5 – A summary of evidence has been added to Section 7.2.4 Specific aspects of treatment of CIS.
- Section 7.3.4 – A Summary of evidence has been added to Section 7.3 Treatment failure of intravesical therapy.

2.   METHODS

2.1   Data Identification

For the 2016 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. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews with meta-analysis, randomised controlled trials, and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published during the period from 1st April 2014 to 31st May 2015. Databases covered by the search included Medline, EMBASE and the Cochrane Libraries. A total of 1,040 unique records were identified, retrieved and screened for relevance. A detailed search stratefy is available on line:
https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications.

A section of the text has been updated based on an systematic review and individual patient data meta-analysis:
- 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? [4] (Section 7.2.1.1).

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
The following section was peer reviewed prior to publication:
• Chapter 7 – Disease management

The other sections of the NMIBC Guidelines were peer-reviewed in 2015.

2.3   Future goals
The results on ongoing and new systematic reviews will be included in the 2017 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 reviews:
1. Is there a difference between the 2004 WHO grading system and the 1973 WHO grading system for NMIBC in terms of prognostic performance? [6].
2. Is there a difference between the 2004 WHO grading system and the 1973 WHO grading system for NMIBC in terms of reproducibility?

3.   EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1   Epidemiology
Bladder cancer (BC) is the 7th most commonly diagnosed cancer in the male population worldwide, while it drops to 11th 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 (EU), 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, 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 methodology and 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, CIS) or submucosa (stage T1). They have a high prevalence due to long-term survival in many cases and lower risk of cancer- specific mortality compared to T2-4 tumours [8, 11].

3.2   Aetiology
Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [8, 12-14] (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, processing paint, dye, metal and petroleum products [8, 15-17]. In developed industrial settings, these risks have been reduced by work-safety guidelines so that chemical workers no longer have a higher incidence of BC compared to the general population [18].

While family history seems to have little impact [19] and no overt significance of any genetic variation for BC has been shown to date, genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors [8, 20, 21].

Although the significance of the amount of fluid intake is uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, while exposure to arsenic in drinking water increases risk [8, 11, 22] (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 an NAT2 slow acetylation phenotype [23, 24]. Other dietary habits seem to have little impact [25].

Exposure to ionizing radiation is connected with increased risk; weak association was also suggested for cyclophosphamide and pioglitazone [8, 11] (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 text is limited to urothelial carcinoma, unless specified otherwise.

3.4 Summary of evidence

	LE
Worldwide, bladder cancer is the 11th most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC diagnosis have been identified.	3

BC = bladder cancer.

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. 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) and/or 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. The terms "NMIBC" and "superficial BC" are therefore suboptimal descriptions.

4.2 Tumour, Node, Metastasis Classification (TNM)

The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) was updated in 2009 (7th Edn.), but with no changes for bladder tumours (Table 4.1) [26].

Table 4.1: 2009 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 *in situ*: '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, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N - 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 lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	

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

In 2004, the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) published a new histological classification of urothelial carcinomas which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [27, 28] (Tables 4.2, 4.3, Fig 4.1). Recently an update of the WHO grading classification was published, but the following guidelines are still based on the 2004 WHO classification [28, 29].

Table 4.2: WHO grading in 1973 and in 2004 [27, 28]

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004 WHO grading system [papillary lesions]
Urothelial papilloma (completely benign lesion)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma

The prognostic value of both WHO 1973 and 2004 grading systems has been confirmed. Attempts to demonstrate better prognostic value of one of them, however, have yielded controversial results [30-35]. (LE: 2a). Moreover the WHO 2004 systems 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]*
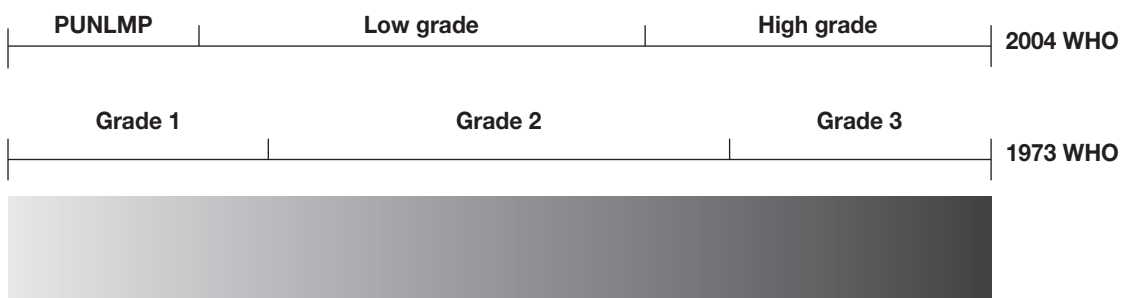
Histologic Spectrum of urothelial carcinoma [UC]
1973 WHO Grade 1 carcinomas have been reassigned to papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade (LG) carcinomas in 2004/2016 WHO classification, and Grade 2 carcinomas to LG and high-grade (HG) carcinomas. All 1973 WHO Grade 3 carcinomas have been reassigned to HG carcinomas (Reproduced with permission from Elsevier).
PUNLMP = papillary urothelial neoplasm of low malignant potential; WHO = World Health Organization.

4.4 CIS and its classification

Carcinoma *in situ* (CIS) is a flat, high-grade, non-invasive urothelial carcinoma. It can be missed at cystoscopy or be considered as an inflammatory lesion if it is 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 [36].

Classification of CIS into clinical type [37]:
* 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

- 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

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

There is significant variability among pathologists for diagnosis of CIS, for which agreement is achieved in only 70-78% of cases [38, 39] (LE: 2a). There is also interobserver variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1997 and 2004 classifications. The general conformity in staging and grading is between 50% and 60% [34, 38-43] (LE: 2a). The published comparisons have not clearly confirmed that the WHO 2004 classification has better reproducibility than the 1973 classification [31, 34, 44].

4.6 Further promising pathology parameters

Some novel parameters based on pathological investigation of resected tissue have been considered for subclassification and prognostic purposes. In T1 tumours, the depth and extent of invasion into the lamina propria (T1 substaging) can be evaluated. The prognostic value of this evaluation has been demonstrated by some retrospective cohort studies [45-48] (LE: 3); nevertheless, it is not recommended in the WHO classification.

According to a meta-analysis of retrospective trials, the presence of lymphovascular invasion (LVI) in TURB specimens was connected with increased risk of pathological upstaging [49] (LE: 3). Lymphovascular invasion has been reported as an unfavourable prognostic factor in T1 tumours [50] (LE: 3).

Some variants of urothelial carcinoma (micropapillary, plasmocytoid, nested, sarcomatoid, microcystic, squamous and adeno variants of urothelial carcinoma etc.), have a poor prognosis [49, 51-57] (LE: 3).

Molecular markers, particularly FGFR3 mutation status, are promising but need further validation [32, 48, 58-60].

4.7 Summary of evidence – classification

	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 have high malignant potential, the term NMIBC is therefore a suboptimal description.	3
For histological classification of NMIBC, the WHO 1973 and 2004 grading systems are used.	2a

CIS (Tis) = carcinoma in situ; NMIBC = non-muscle invasive bladder cancer; TNM = Tumour, Node, Metastasis (classification); WHO = World Health Organization.

4.8 Recommendations for bladder cancer classification

Recommendation	GR
For classification of the depth of tumour invasion (staging) use the 2009 TNM system.	A
For histological classification, use the 1973 and 2004/2016 WHO grading systems.	A
Do not use the term "superficial bladder cancer".	A
Whenever you use the terminology NMIBC in individual cases, mention the tumour stage and grade.	A

TNM = Tumour, Node, Metastasis (classification); WHO = World Health Organization.

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. CIS might be suspected in patients with "storage" lower urinary tract symptoms.

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, which can be seen as filling defects or indicated by hydronephrosis.

Intravenous urography (IVU) can be an alternative if CT is not available [61] (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 [62-64] (LE: 2a). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [63] (LE: 2b). The risk of UTUC during follow up increases in patients with multiple- and high-risk tumours [65] (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 [62] (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%) [66]. The sensitivity in CIS detection is 28-100% [67] (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 [68]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, but in experienced hands specificity exceeds 90% [69] (LE: 2b).

Urine collection should respect the recommendation provided in Section 5.10. One cytospin slide from the sample is usually sufficient [70]. In patients with suspect cytology it is reasonable to repeat the investigation [71] (LE: 3).

5.6 Urinary molecular marker tests
Driven by the low sensitivity of urine cytology, numerous urinary tests were developed [69, 72-79]. None of these markers have been accepted for diagnosis or follow-up in routine practice or clinical guidelines. Some urine tests that have been evaluated in several laboratories/centres and with sufficient numbers of patients are 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 [69, 73-82] (LE: 3).
- Benign conditions and BCG influence many urinary marker tests [69, 72-79] (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]) [73-76] (LE: 3).
- Patient selection explains the wide range in performance of the markers listed in Table 5.1.
- Unlike other urine tests, false-positive results of UroVysion and microsatellite analysis can be attributed to occult disease and these markers therefore identify patients likely to experience early recurrence [83-87] and possibly progression [88] (LE: 3).

Table 5.1: Summary of main 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.

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 [89, 90]. The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness [76, 87, 89, 90]. Routine application of screening is not recommended.

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 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 this high specificity and are not recommended for primary detection.

5.7.3 Surveillance of NMIBC
Research has been carried out into the usefulness of urinary cytology vs. markers in the follow-up of NMIBC [76, 78, 91, 92].

5.7.3.1 Follow-up of high-risk NMIBC
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 NMIBC
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 [73, 76] (LE: 3).

According to current knowledge, no urinary marker can replace cystoscopy during follow up or help to lower cystoscopic 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 [93] (LE: 1b). It supports the adjunctive role of a non-invasive urine test performed before follow-up cystoscopy [93].

5.8 Cystoscopy
The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. CIS is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies [94]. Cystoscopy is initially performed in the office. A flexible instrument with topical intra-urethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [95].

Figure 5.1: Bladder diagram
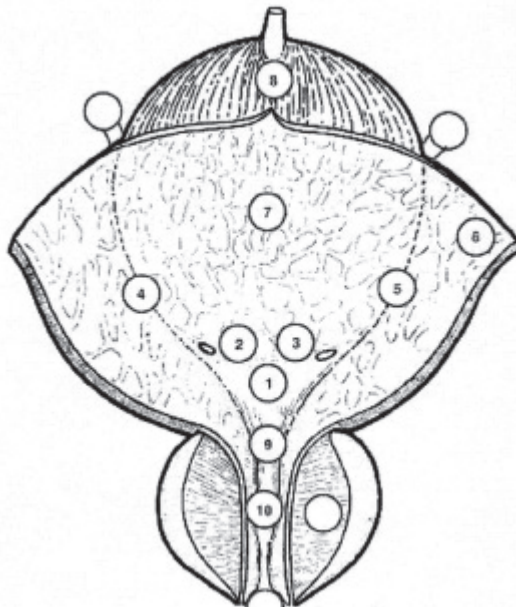
1 = Trigone	6 = Anterior wall
2 = Right ureteral orifice	7 = Posterior wall
3 = Left ureteral orifice	8 = Dome
4 = Right wall	9 = Neck
5 = Left wall	10 – Posterior urethra

5.9 Summary of evidence – primary asssessment of NMIBC

	LE
The diagnosis of BC depends on cystoscopic examination.	1
Urinary cytology has high sensitivity in high-grade tumours including CIS.	2b

BC = bladder cancer; CIS = carcinoma in situ.

5.10 Recommendations for the primary assessment of NMIBC

Recommendation	GR
Patient history should be taken.	A
Renal and bladder US may be used during the initial work-up in patients with haematuria.	C
At the time of the initial diagnosis of NMIBC, CT urography (or IVU) should be performed in selected cases (e.g., tumours located in the trigone, multiple or high-risk tumours).	B
Cystoscopy is recommended in all patients with symptoms suggestive of BC. 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 (Figure 5.1).	C
Voided urine cytology is advocated as an adjunct to cystoscopy to detect high-grade tumour.	C
Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	C

BC = bladder cancer; CT = computed tomography; IVU = intravenous urography; NMIBC = non-muscle invasive bladder cancer; US = ultrasound.

5.11 Transurethral resection of Ta, T1 bladder tumours
5.11.1 Strategy of the procedure
The goal of TURB in Ta, T1 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 5.16). The strategy of resection depends on the size of the lesion (see Section 5.16).
Separate resection of larger tumours provides good information about the vertical and horizontal extent of the tumour and helps to improve completeness of resection [96, 97] (LE: 3).

A complete and correct TURB is essential to achieve a good prognosis [98]. 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 [97, 99] (LE: 2b). It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [100].

5.11.2 *Office-based fulguration*
In patients with a history of small, Ta LG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis can reduce the therapeutic burden and can be a treatment option [101, 102] (LE: 3). There are no prospective comparative studies assessing the oncological outcomes.

5.11.3 *New resection techniques*
Compared to monopolar resection, the bipolar electrocautery system has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and produce better specimens for the pathologist [103] (LE: 3). Currently, the results remain controversial [104-106].

5.11.4 *Bladder and prostatic urethral biopsies*
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 5.16). The indication for random biopsies reflects the fact, that the likelihood of detecting CIS, especially in low-risk tumours, is extremely low (< 2%) [107] (LE: 2a). The risk increases in patients with high-risk tumours and with positive cytology [108].
If equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy (see Section 5.12.1).
Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.* [109] 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 on the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [110] (LE: 3). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases (see recommendation in Section 5.16) [109, 111].

5.12 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.

5.12.1 *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 [112, 113] (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%) [113]. A prospective randomised trial did not confirm a higher detection rate in patients with known positive cytology before TURB [114].
Photodynamic diagnosis had lower specificity than white-light endoscopy (63% vs. 81%) [113]. False-positivity can be induced by inflammation or recent TURB and during the first 3 months after BCG instillation [115, 116] (LE: 3). Prospective randomised studies evaluating the impact of ALA fluorescence-guided (FC) TURB on disease-recurrence rate provided controversial results [113, 117, 118].
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 HAL arms an increase in detection of tumour lesions across all risk groups and an absolute reduction of < 10% in recurrence rates within 12 months [119] (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 [120, 121]. The value of FC for improvement of outcome in relation to progression rate, survival and clinical management remains to be demonstrated.

5.12.2 **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 [122, 123] (LE: 3). The suggested reduction of recurrence rate if NBI is used during TURB has not yet been fully confirmed [124].

5.13 Second resection
The significant risk of residual tumour after initial TURB of Ta, T1 lesions has been demonstrated [98] (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-55% of patients, and after resection of TaG3 tumour in 41.4% [125-129]. Moreover, the tumour is often understaged by initial resection. The likelihood that muscle-invasive disease is detected by second resection of initially T1 tumour ranges from 4-25%, and it increases to 45% if there was no muscle in the initial resection [114]. This risk increased to 50% in some radical cystectomy (RC) series, although these studies only enrolled selected patients [130-132] (LE: 2a). Treatment of a Ta, T1 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 [125, 126] (LE: 2a), improve outcomes after BCG treatment [133] (LE: 3) and provide prognostic information [130, 134] (LE: 3). Based on these arguments, a second TURB is recommended in selected cases (see Section 5.16).

5.14 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 recommended. A high quality of resected and submitted tissue is essential for correct pathological assessment. The presence of sufficient muscle is necessary for the correct assignment of T category. To obtain all required information, the specimen collection, handling and evaluation should respect the recommendations provided below (see Section 5.16) [135].

5.15 Summary of evidence - TURB and pathology report

	LE
TURB followed by pathology investigation of the obtained specimen(s) is an essencial 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, Ta LG/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.	

BCG = bacillus Calmette-Guérin; TURB = transurethral resection of the bladder.

5.16 Recommendations for TURB and/or biopsies and pathology report

Recommendation	GR
In patients suspected of harbouring bladder cancer TURB followed by pathology investigation of the obtained specimen(s) is recommended as a diagnostic procedure and initial treatment step.	A
Perform TURB systematically in individual steps: • 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 prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • surgical report formulation; • precise description of the specimen for pathology evaluation.	C
Performance of individual steps:	
Perform resection in one piece for small papillary tumours (< 1 cm), including part from the underlying bladder wall.	B
Perform resection in fractions including the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area for tumours > 1 cm in diameter.	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 walls) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance). If equipment is available, use PDD-guided biopsies.	B
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder CIS 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 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
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 a UTUC, CIS in the bladder (random biopsies or PDD-guided biopsies) and tumour in prostatic urethra (prostatic urethra biopsy).	C
Perform a second TURB in the following situations: • after incomplete initial TURB; • if there is no muscle in the specimen after initial resection, with exception of TaG1 tumours and primary CIS; • in all T1 tumours; • in all HG/G3 tumours, except primary CIS.	A
If indicated, perform a second TURB within 2-6 weeks after initial resection. It should include the resection of primary tumour site.	C
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 LVI or unusual (variant) histology.	C
In difficult cases, consider an additional review by an experienced genitourinary pathologist.	B

CIS = carcinoma in situ; LVI = lymphovascular invasion; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder; UTUC = upper tract urothelial carcinoma.

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 Ta, T1 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 [136]. The basis for these tables are individual patient data from 2,596 patients diagnosed with Ta, T1 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, as in the original article [136], into four categories that reflect various probabilities of recurrence and progression at 1 and 5 years (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 iPhone, iPad 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 12 instillations over 5-6 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:
- sex;
- 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 [137] (LE: 2a). The lower risks in the CUETO tables may be attributed to using BCG, 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 [138, 139] (LE: 2a).

In 1,812 intermediate- and high-risk patients without CIS treated with 1 to 3 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 overall survival (OS). T1G3 patients do poorly, with 1- and 5-year disease-progression rates of 11.4% and 19.8%, respectively. Using these data the new EORTC risk tables for BCG treated patients were designed [140] (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 patients treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with induction course only) [109] [141] (LE: 2b).
- Attention must be given to patients with T1G3 tumours in bladder (pseudo) diverticulum because of an absence of muscle layer in the diverticular wall [142] (LE: 3).
- In patients with high-risk disease, the tumour stage at the time of the 2nd TURB is an unfavourable prognostic factor [130, 134] (LE: 3)
- In patients with T1G2 tumours treated with TURB, recurrence at 3 months was the most important predictor of progression [143] (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 [138, 144].

6.2 Carcinoma *in situ*
Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [145] (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 [146, 147], in extended CIS [148] and in CIS in the prostatic urethra [109] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [137-139, 143]. Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders [149, 150] (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.

Table 6.3: Risk group stratification

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, Ta, G1* (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: • T1 tumour • G3** (HG) tumour • CIS • Multiple and recurrent and large (> 3 cm) Ta, G1G2 tumours (all conditions must be presented in this point)*

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)
CIS = carcinoma in situ; HG = high-grade; LG = low-grade; PUNLUMP = Papillary urothelial neoplasm of low malignant potential.

6.4   Summary of evidence - stratification of NMIBC

	LE
The EORTC scoring system and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with 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.	
Patient age and grade are the most important prognostic factors for OS.	

BCG = bacillus Calmette-Guérin; CUETO = Club Urológico Español de Tratamiento Oncológico;
EORTC = European Organization for Research and Treatment of Cancer; OS = overall survival.

6.5   Recommendations for stratification of NMIBC

Recommendation	GR
Stratify patients into three risk groups according to Table 6.3.	B
Apply EORTC risk tables and calculator for individual prediction of the risk of tumour recurrence and progression in different intervals after TURB.	B
For individual prediction of the risk of tumour recurrence and progression in patients treated with BCG use the CUETO risk tables and the new EORTC risk tables.	B

BCG = bacillus Calmette-Guérin; CUETO = Club Urológico Español de Tratamiento Oncológico;
EORTC = European Organization for Research and Treatment of Cancer; TURB = transurethral resection of the bladder.

7.   DISEASE MANAGEMENT

7.1   Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression [151, 152] (LE: 3). While it is still controversial whether smoking cessation in bladder cancer will favourably influence the outcome of BC treatment, patients should be counselled to stop smoking due to the general risks connected with tobacco smoking [153-156] (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 3-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [98]. 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 (chemoresection) on residual tumour cells at the resection site and on small overlooked tumours [157-160] (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 [4, 161-163] (LE: 1a). In the most recent systematic review and individual patient data meta-analysis of 2,278 eligible patients [4], SI reduced the 5-year recurrence rate by 14%, from 59% to 45%. The number to treat (NNT) to prevent one recurrence within 5 years was 7 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 in these two subgroups of patients. Mitomycin C (MMC), epirubicin, and pirarubicin have all shown a beneficial effect [4]. No randomised comparisons of individual drugs are have been conducted [4, 161-163] (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 [157, 164-166] (LE: 3). In all SI studies, the instillation was administered within 24 hours. To maximize 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 2 hours in the recovery room or even in the operating theatre.

As severe complications have been reported in patients with drug extravasation [167, 168] 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 [161] (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. 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 [169-171] (LE: 2a). In one study [172], 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 [169, 171].

A large meta-analysis of 3,703 patients from 11 randomised trials showed a highly significant 44% reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [173]. 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 [174, 175] (LE: 1a) (see Section 7.2.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [176-178] (see Section 7.2.2) (LE: 1a). However, BCG causes significantly more side effects than does chemotherapy [178] (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 [171]. 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 [179] (LE: 1b). Another trial reported that a 1-hour instillation of MMC was more effective than 30 minutes instillation, but no efficacy comparisons are available for 1- and 2-hour instillations [180] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [181] (LE: 1b). In view of these data, instructions are provided (see Section 7.5).

7.2.1.3.2   Microwave-induced hyperthermia and electromotive drug administration (EMDA)
Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia or the efficacy of MMC using electromotive drug administration (EMDA) in patients with high-risk tumours. The current evidence, however, is limited [182-184] and both treatment modalities are considered to be experimental (LE: 2b).

7.2.1.4   *Summary of evidence - intravesical chemotherapy*

	LE
In patients with NMIBC and prior low recurrence rate (less than or equal to one recurrence per year) and in those with an EORTC recurrence score < 5, SI significantly reduces the recurrence rate compared to TURB 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

EORTC = European Organization for Research and Treatment of Cancer; SI = single instillation;
TURB = transurethral resection of the bladder.

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 [176, 185-188] (LE: 1a). Three recent RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin + interferon [189], MMC [190], or epirubicin alone [177] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long-lasting [177, 190] and was also observed in a separate analysis of patients with intermediate-risk tumours [177].

One meta-analysis [176] 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 prevents, or at least delays, the risk of tumour progression [174, 175] (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 Ta, T1 papillary tumours and in those with CIS [175]. 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 [177] (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 [176].

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 [191]. 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 [176] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 years of age, but it was still more effective than epirubicin [192] (LE: 1a).

7.2.2.2   *BCG strain*
The EORTC meta-analysis suggested no large differences in efficacy between various BCG strains [175]. Recently published smaller studies without maintenance demonstrated some differences between strains. This clearly needs further evaluation in prospective trials [193, 194] (LE: 2a).

7.2.2.3   *BCG toxicity*
BCG intravesical treatment is associated with more side effects compared to intravesical chemotherapy [175]

(LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [195] (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 [195]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [196].

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 [197, 198] (LE: 3).

BCG should be used with caution (relative contraindication) in immunocompromised patients (immunosuppression, human immunodeficiency virus [HIV] infection) [199], 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 [200-202] (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 [203, 204] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [204-207]

Management options for local side effects (modified from IBCG group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or NSAIDs
	If symptoms improve within a few days: continue instillations

	If symptoms persist or worsen:
	  a. Postpone the instillation
	  b. Perform a urine culture
	  c. Start empirical antibiotic treatment

	If symptoms persist even with antibiotic treatment:
	  d. With positive culture: antibiotic treatment according to sensitivity
	  e. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [205].

	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 3 months.
	Cessation of intravesical therapy.
Epididymo-orchitis [206]	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 [207].
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 > two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.

BCG sepsis	Prevention: initiate BCG at least 2 weeks post-TURB (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • 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 *Enterococcus*.
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

BCG = bacillus Calmette-Guérin; IBCG = International Bladder Cancer Group; NSAID = non-steroidal antiinflammatory drug; TURBT = transurethral resection of bladder tumour.

7.2.2.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales [208]. For optimal efficacy, BCG must be given in a maintenance schedule [174-176, 188] (LE: 1a). Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks to 27 over 3 years [209]. The EORTC meta-analysis was unable to determine which BCG maintenance schedule was the most effective [175]. 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 [174] (LE: 1a).

The optimal number of induction instillations and optimal frequency and duration of maintenance instillations is not fully known. Moreover, it can be different in each individual patient [210]. In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, 3 years' maintenance (three-weeky 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 3-year arm, however, 36.1% of patients did not complete the 3-years schedule [211] (LE: 1b). In a RCT of 397 patients CUETO suggested that in high-risk tumours, the maintenance schedule with only 1 instillation every 3 months for 3 years may be suboptimal [212] (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 [213, 214] (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 [215] (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 [196, 211] (LE: 1b). Moreover, the routine application is complicated by potential technical difficulties in preparing the reduced dose reliably.

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-muscle-invasive-bladder-cancer/?type=appendices-publications.

7.2.2.7 Summary of evidence - BCG treatment

	LE
In patients with intermediate- and high-risk tumours, intravesical 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 in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

BCG = bacillus Calmette-Guérin; TURB = transurethral resection of the bladder.

7.2.3 Combination therapy
In one RCT, a combination of MMC and BCG reduced recurrences but was more toxic compared to BCG monotherapy. Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by one MMC instillation [216]. Another RCT demonstrated that in frequently recurrent NMIBC significantly higher efficacy of weekly MMC followed by monthly BCG in reduction of the recurrence rate when compared to BCG and interferon [217]. In the 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 [183].

7.2.4 Specific aspects of treatment of CIS
7.2.4.1 Treatment strategy
The detection of concurrent CIS increases the risk of recurrence and progression of Ta, T1 tumours [136, 137], 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 CIS must be followed by further treatment, either intravesical BCG instillations or radical cystectomy (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 [145] (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 [145-148, 218] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [148, 209, 218, 219] (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 alone. 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 [220] (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression (a subgroup of 403 patients with CIS), BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different immunotherapy [175] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [221]. 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 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 [222]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [222] (LE: 3).

In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [36]. 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 [95, 223] (LE: 3).

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 [223, 224] (LE: 3). Treatment of CIS that involves the UUT is discussed in the Guidelines on Urothelial Tumours of the Upper Urinary Tract [1].

7.2.4.5 Summary of evidence – treatment of CIS

	LE
CIS cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical 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.	1b

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ.

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

TURB

Consider tumour appearance and early postoperative situation

Presumably low- or intermediate-risk tumour with low previous recurrence rate (≤ 1 recurrence per year) and EORTC recurrence score < 5

No perforation, no extensive resection, no bleeding with clots after TURB

Apparently muscle-invasive or high-risk tumour (sessile appearance etc.)

Bladder perforation, bleeding with clots

Single installation of chemotherapy (GR: A)

Consider completeness of the resection and pathological report:

Incomplete resection or no muscle (except for monofocal TaG1/LG) or T1 or G3/HG (except for primary CIS)

Macroscopically complete resection and TaG1-2/LG with muscle in the specimen or in TaG1/LG even without muscle or in primary CIS

Muscle invasive tumour

See guidelines for MIBC

second TURB (GR: A) in 2-6 weeks (GR: C)

Stratify patients into risk groups (GR: B)
• Previous history
• Endoscopic appearance (number and size of tumours)
• Pathological report the worst stage and grade from either or second TURB (GR: B)

Low-risk tumour (primary solitary TaG1/LG < 3 cm)

Intermediate-risk tumour

High-risk tumour (T1 or Tis or G3/HG or multiple and recurrent and > 3 cm TaG1-2/LG)

Cystoscopy (GR: A) at 3 mo

If negative, cystoscopy (GR: A) at 12 mo and then yearly for 5 yr (GR: C)

Primary or recurrent tumour without previous chemotherapy: Intravesical BCG for 1 yr (6 weekly and 3 weekly at 3, 6 and 12 mo) or intravesical chemotherapy for up to 12 mo (GR: A)

Recurrent tumour with previous chemotherapy: Intravesical BCG for 1 yr (6 weekly and 3 weekly at 3, 6 and 12 mo) (GR: A), in late recurrence of small TaG1/LG consider repeating intravesical Chemotherapy

In all cases: Cystoscopy (GR: A) and cytology (GR: B) at 3 mo If negative, cystoscopy and cytology at 3-6 mo intervals until 5 yr and then yearly (GR: C)

Highest-risk tumour (T1G3/HG+CIS, T1G3/HG+CIS in prostatic urethra, multiple T1G3/HG, T1G3/HG > 3 cm, micropapillary variant)

Positive or suspect cystoscopy during follow-up

No

Yes

Explain the risk and consider radical cystectomy

Tiny papillary recurrence

Larger or non papillary recurrence

Intravesical BCG for 1-3 yr (GR: A)

Cystoscopy (GR: A) and cytology (GR: B) at 3 mo

If negative, cystoscopy and cytology every 3 mo for 2 yr, every 6 mo thereafter until 5 yr and then yearly (GR: C), CT-IVU or IVU yearly (GR: C)

Consider patients' age, comorbidities and preferences

Positive or suspect cystoscopy during follow-up

Office fulguration or surveillance

Positive cytology with no visible tumour in the bladder during follow-up

Follow-up: cystoscopy (GR: A) Schedule: individual (GR: C)

TURB + biopsies from abnormal looking mucosa (GR: B), bladder random biopsies if indicated* (GR: C), prostatic urethra biopsy if indicated* (GR: C) (See text in guidelines)

Re-check upper tract (GR: B)

Bladder random biopsies (GR: B), prostatic urethra biopsy in men (GR: B), if available use PDD (GR: B)

Consider pathological report

Non-muscle invasive recurrence

Muscle invasive recurrence

Consider previous history and pathological report (see flow-chart II)

See MIBC guidelines

*For details and explanations see the text of the guidelines
BCG = bacillus Calmette-Guérin; 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 non-muscle-invasive recurrence of BC after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillation [176] (LE: 1a).

7.3.2 *Recurrence and failure after intravesical 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 3 months [225]. Further conservative treatment with BCG is associated with increased risk of progression [149, 226] (LE: 3).   2. If CIS (without concomitant papillary tumour) is present at both 3 and 6 months. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [36] (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 [227] (LE: 3).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing induction [204].

* Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; WHO = World Health Organization.

7.3.3 *Treatment of BCG failure and recurrences after BCG*

Treatment recommendations are provided in Section 7.5 and Table 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 [228, 229] (LE: 3). Additionally, there are now several bladder preservation strategies available that can be categorised as immunotherapy [230] chemotherapy, device-assisted therapy (see 7.2.1.3.2), and combination therapy (see 7.2.3) [231]. Changing from BCG to these options can yield responses in selected cases with BCG treatment failure [228, 232-239] (LE: 3).

Treatments other than RC must be considered oncologically inferior in patients with BCG failure at the present time [149, 225, 226] (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*

	LE
Prior intravesical chemotherapy has no impact on the effect of BCG instillation.	1a
Treatments other than radical cystectomy must be considered oncologically inferior in patients with BCG failure.	3

BCG = bacillus Calmette-Guérin.

Flowchart 7.2: Treatment strategy in recurrence during or after intravesical BCG*
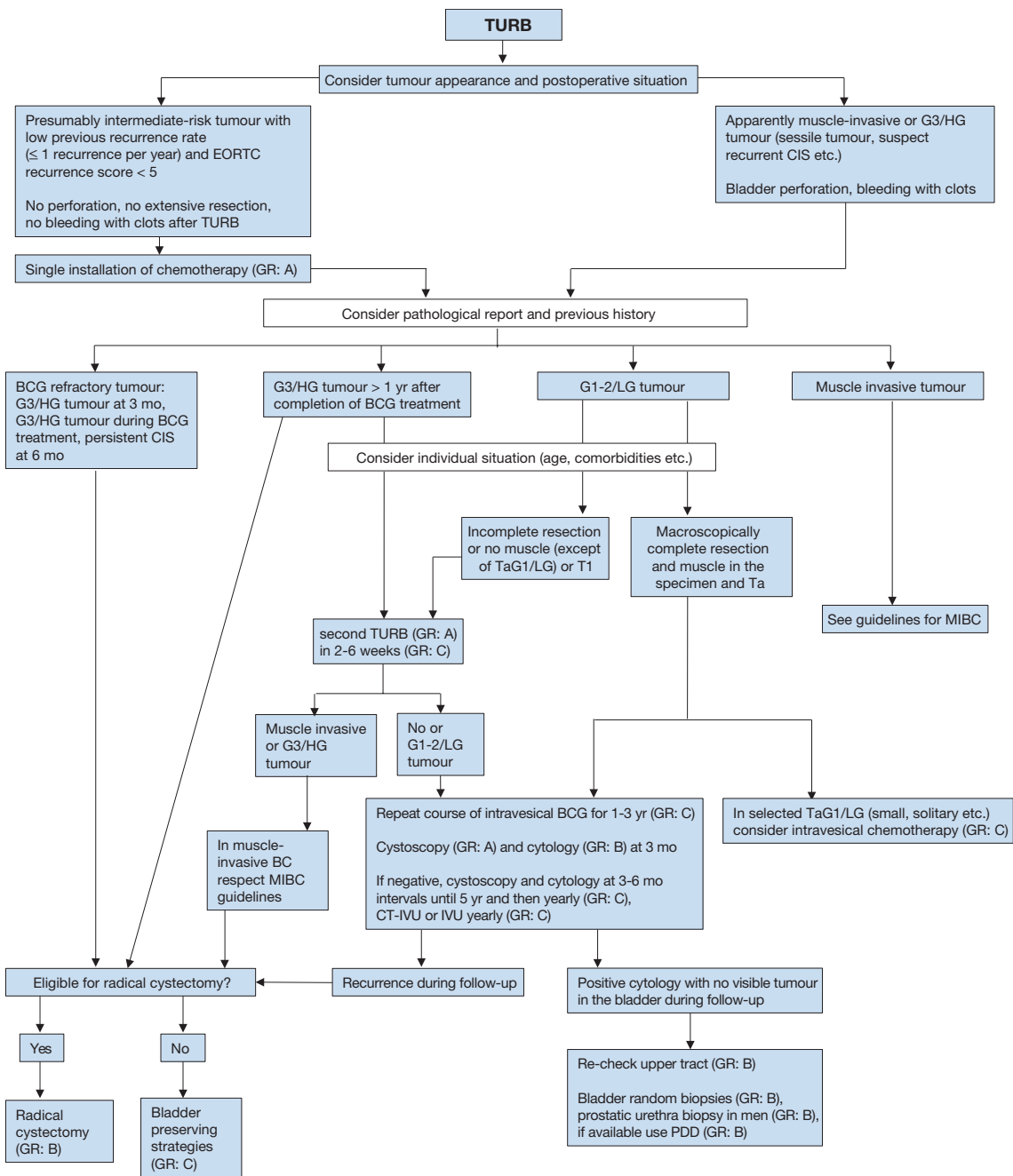
For details and explanations, see the text of the guidelines.
BCG = bacillus Calmette-Guérin; HG = high-grade; IVU = intravenous urography; LG = low-grade;
PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

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 (after BCG failure) procedure.

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 [111, 131, 240-245] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).

The potential benefit of RC must be weighed against the risk, 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 progression (see

Section 7.6) [49, 109, 136, 137, 246] (LE: 3).

The benefits and risks of immediate and delayed RC should be discussed with patients. Individual additional prognostic factors in T1 tumours mentioned in Sections 6.1 and 4.6 should be considered.

Early RC is strongly recommended in patients with BCG-refractory tumours, as mentioned above. A delay in RC might lead to decreased disease-specific survival [247] (LE: 3). In patients in whom RC is performed at the time of pathological NMIBC, the 5-year disease-free survival rate exceeds 80% [248-252] (LE: 3).

7.5 Recommendations for adjuvant therapy in Ta, T1 tumours and for therapy of CIS

LG = low-grade;	GR
Smokers with confirmed NMIBC should be counseled to stop smoking.	B
The type of further therapy after 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 (less than or equal to 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), 1-year full-dose BCG treatment (induction plus 3 weekly instillations at 3,6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 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 1-3 years (induction plus 3 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, TUR of the prostate followed by intravesical instillation of BCG can be offered.	C
In patients at highest risk of tumour progression (Section 7.6), immediate radical cystectomy should be considered.	C
In patients with BCG failure, radical cystectomy is indicated.	B
Intravesical chemotherapy	
One immediate instillation of chemotherapy should be administered within 24 hours after TURB, preferably within 2 hours.	C
One immediate instillation of chemotherapy should be omitted in any case of overt or suspected intra- or extra-peritoneal perforation (after extensive TURB, 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 1 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 1-2 hours.	C
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first 2 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 (Table 7.1).	C

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; TUR = transurethral resection;
TURB = transurethral resection of the bladder.

7.6 Treatment recommendations in Ta, T1 tumours and CIS according to risk stratification

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, Ta, G1/PUNLMP, LG, < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All cases between categories 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 1-year full-dose BCG treatment (induction plus 3-weekly instillations at 3,6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 year.
High-risk tumours	Any of the following: • T1 tumours; • HG/G3 tumours; • CIS; • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumours (all these conditions must be presented).	Intravesical full-dose BCG instillations for 1-3 years or cystectomy (in highest-risk tumours - *see below*).
	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, unusual histology of urothelial carcinoma, LVI (see Sections 4.6 and 6.2).	Radical cystectomy should be considered, in those who refuse intravesical full-dose BCG instillations for 1-3 years.
	BCG failures.	Radical cystectomy is recommended.

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade; LG = low-grade; LVI = lymphovascular invasion; TURB = transurethral resection of the bladder.

7.7 Treatment recommendations for BCG failure and recurrences after BCG

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

BCG = bacillus Calmette-Guérin; HG = high-grade.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need to be followed up. 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 [136, 137].

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, Ta LG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [253-257] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be a safe option that reduces the therapeutic burden [101] (LE: 3). Some authors have even defended temporary surveillance in selected cases [256-258] (LE: 3).
*   The first cystoscopy after TURB at 3 months is an important prognostic indicator for recurrence and progression [143, 149, 259-261] (LE: 1a). Therefore, the first cystoscopy should always be performed 3 months after TURB in all patients with Ta, T1 tumours and CIS.
*   In tumours at low-risk, the risk of recurrence after 5 recurrence-free years is low [260] (LE: 3). Discontinuation of cystoscopy or its replacement with less-invasive methods can be considered [261].
*   In tumours originally intermediate- or high-risk, recurrences after 10 years tumour-free are not unusual [262] (LE: 3). Therefore, life-long follow-up is recommended [261].
*   The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT)
*   The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [65] (LE: 3).
*   Positive urine test results have a positive impact on the quality of performed follow-up cystoscopy [93] (LE: 1b). It supports the adjunctive role of urine tests during follow-up.

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 that have investigated 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 [94]. The following recommendations are based mostly on retrospective data.

8.1 Summary of evidence - follow-up of patients with NMIBC

	LE
The first cystoscopy after TURB at 3 months is an important prognostic indicator for recurrence and progression.	1a
The risk of UUT recurrence increases in patients with multiple- and high-risk tumours.	3

TURB = transurethral resection of the bladder; UUT = upper urinary tract.

8.2 Recommendations for follow-up in patients after TURB of NMIBC

Recommendations	GR
The follow-up of Ta, T1 tumours and CIS is based on regular cystoscopy.	A
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	C
Patients with high-risk tumours should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	C
Patients with intermediate-risk Ta tumours should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C
Regular (yearly) upper tract imaging (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 R-biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 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

CIS = carcinoma in situ; CT-IVU = computed tomography intravenous urography; IVU = intravenous urography; PDD = photodynamic diagnosis; R-biopsies = random biopsies.

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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. 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 Urothelial Carcinomas of the Upper Urinary Tract

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1. INTRODUCTION

1.1   Aims and objective
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).

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.

1.2   Panel composition
The European Association of Urology (EAU) Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including 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-tract-urothelial-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 can be viewed on the EAU website: 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 2016 EAU guidelines on UTUC presents an update of the 2015 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 2016 print:
Changed or new conclusions and recommendations can be found in sections:
*   Section 6.2 Molecular markers has been added as a new topic.
*   Section 6.4 Bladder recurrence has been added as a new topic.

New recommendations have been included in Chapter 6 - Prognosis

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 lymphocascular invasion.	3

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

MSI = Microsatellite instability.

*   In section 7.1.2.1 Laparoscopic radical nephrectomy, the findings of the Systematic review have been included (see below).
*   Section 7.2.2 Systemic chemotherapy has been expanded.
*   A new algorithm - Figure 7.2 Surgical treatment according to location and risk status - has been included.

2. METHODS

2.1 Data identification

For the 2016 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. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews with meta-analysis, randomised controlled trials, and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published during the period from 1st April 2014 to 31st May 2015. Databases covered by the search included Medline, EMBASE and the Cochrane Libraries. A total of 1,040 unique records were identified, retrieved and screened for relevance. The search strategy is published online: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?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 [1]. 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 as the above address.

2.2 Review

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

2.3 Future goals

The results on ongoing and new systematic reviews will be included in the 2017 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 UTUC.
- What are the oncological outcomes of kidney-sparing surgery versus radical nephroureterectomy for the treatment of upper tract urothelial carcinoma? [2].
- What are the benefits and harms of lymph node dissection (LND) during radical nephroureterectomy for upper tract urothelial carcinoma (UTUC)? [3].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Urothelial carcinomas (UCs) are the fifth most common tumours [4]. 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 [5]. In contrast, UTUCs are uncommon and account for only 5-10% of UCs [4, 6]. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer is present [7]. Recurrence in the bladder occurs in 22-47% of UTUC patients [8], compared with 2-6% in the contralateral upper tract [9, 10].
Approximately 60% of UTUCs are invasive at diagnosis compared with 15-25% of bladder tumours [11, 12]. UTUCs have a peak incidence in people aged 70-90 years and are three times more common in men [13, 14].
Familial/hereditary UTUCs are linked to hereditary non-polyposis colorectal carcinoma (HNPCC) [15], which can be screened for during interview (Figure 3.1) [16]. Patients should undergo DNA sequencing to identify hereditary cancers misclassified as sporadic if they fulfil the criteria for HNPCC [15, 17].

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

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                    ┌──────────────┐
                    │     UTUC     │
                    └──────┬───────┘
                           │
           ┌───────────────────────────────────┐
           │ Systematic screening during medical interview │
           └───────────────┬───────────────────┘
                           │
        ┌──────────────────┴───────────────────────┐
        │                                           │
┌───────────────────────────────────┐    ┌──────────────────┐
│ Suspicion of hereditary UTUC       │    │  Sporadic UTUC   │
│ (10-20%)                           │    │   (80-90%)       │
│ - Age < 60 yr                      │    └──────────────────┘
│ - Personal history of HNPCC-       │
│   spectrum cancer                  │
│           or                       │
│ - First-degree relative < 50 yr    │
│   with HNPCC-spectrum cancer       │
│           or                       │
│ - Two first-degree relatives with  │
│   HNPCC-spectrum cancer            │
└───────────────┬───────────────────┘
                │
┌───────────────────────────────────┐
│ Germ-line DNA sequencing: mutation?│
└───────────────┬───────────────────┘
                │
┌───────────────────────────────────┐
│ - Clinical evaluation for other    │
│   HNPCC-related cancer:            │
│   colorectal, gastrointestinal,    │
│   endometrial ovarian and skin     │
│ - Close monitoring and follow-up   │
│ - Familial genetic counselling     │
└───────────────────────────────────┘
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HNPCC = hereditary non-polyposis colorectal carcinoma.

3.2 Risk factors

Various environmental risk factors contribute to UTUC development [18, 19]. Tobacco exposure increases the relative risk from 2.5 to 7 [20, 21]. Historically, UTUC 'amino tumours' were related to occupational exposure to carcinogenic aromatic amines. However no specific risk factors for UTUC have been suggested compared to bladder cancer.

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. The odds ratio of developing UC after exposure to aromatic amines is 8.3 [19, 21]. Upper tract urothelial tumours caused by phenacetin consumption almost disappeared after the product was banned in the 1970s [19].
     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 [19, 22, 23].
     There is a high incidence of UTUC in Taiwan, especially on the South-west coast which represents 20-25% of UCs in the region [19, 23]. There is a possible association of UTUC with blackfoot disease and arsenic exposure in drinking water in this population [19, 23, 24].

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. Only two UTUC-specific polymorphisms have been reported [25, 26].

3.3 Histology and classification

3.3.1 *Histological types*

There are morphological variants of UTUC. These variants always correspond to high-grade tumours with worse prognosis compared to pure UC. Those variants are: micropapillary, plasmacytoid, small cell carcinoma (neuroendocrine) or lymphoepithelial variants [27, 28].

Upper tract urothelial carcinoma with pure non-urothelial histology is an exception [29, 30] but variants are present in ~25% of cases [31] [31, 32]. 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 [27, 28].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and bladder carcinoma are similar [11]. 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.

4.2 Tumour Node Metastasis staging

The Tumour Node Metastasis (TNM) classification is shown in Table 4.1 [33]. 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 in the pTNM staging system [31, 34, 35]. 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 have aggressive pathology and higher risk of disease recurrence [31, 34].

Table 4.1: TNM classification 2009 for upper tract urothelial carcinoma [33]

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
	Ta Non-invasive papillary carcinoma
	Tis Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
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 but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.3 Tumour grade

Until 2004, the World Health Organization (WHO) classification of 1973 was used most often, which distinguished only three grades (G1-G3) [36, 37]. The 2004 WHO classification considers histological data to distinguish non-invasive tumours: papillary urothelial neoplasia of low malignant potential, and low-grade and high-grade carcinomas (low grade vs. high grade). Only few tumours of low malignant potential are found in the upper urinary tract [27, 28].

4.4 Guidelines for staging and classification systems

Recommendation	LE	GR
Classify the depths of invasion (staging) according to TNM classification.	3	A
Classify flat, high-grade tumours, confined to the mucosa, as CIS (Tis).	3	A
Use the WHO 1973 and 2004 grading systems for the histological classification of UTUC.	3	A

CIS (Tis) = carcinoma in situ; TNM = Tumour, Node, Metastasis (classification); WHO = World Health Organization.

5. DIAGNOSIS

5.1 Symptoms

The most common symptom is visible- or non-visible haematuria (70-80%) [38, 39]. Flank pain occurs in 20-40% of cases, and a lumbar mass in 10-20% [40, 41]. 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 [40, 41].

5.2 Diagnosis
5.2.1 *Imaging*
5.2.1.1 *Computed tomography urography*
Computed tomography urography (CTU) has the highest diagnostic accuracy for the diagnosis of UTUC [41]. The sensitivity of CTU for UTUC is 0.67-1.0 and the specificity is 0.93-0.99 [42-49].

Computed tomography urography is defined as CT examination of the kidneys, ureters and bladder following the administration of intravenous contrast material and includes several phases of image acquisition. [50]. 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 [51, 52].

Flat lesions are not detectable unless they exert a mass effect or cause urothelial thickening [53].

The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [50, 54, 55]. The presence of enlarged lymph nodes is highly predictive of metastasis in UTUC [56].

5.2.1.2 *Magnetic resonance imaging*
Magnetic resonance urography (MRU) is indicated in patients who cannot undergo CTU, 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 in the bladder or prostatic urethra CIS has been detected [11, 58]. Cytology is less sensitive for UTUC than bladder tumours and it should be performed *in situ* in the renal cavities [59].

Retrograde ureteropyelography remains an option to evaluate UTUCs [43, 60]. 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 UTUCs parallels its performance in bladder cancer [61]. However, its use may be limited by the preponderance of low-

grade recurrent disease in the population undergoing surveillance and minimally invasive therapy for UTUCs [62, 63]. FISH appears to have a limited value for surveillance of UTUCs [62, 63].

5.2.3 *Diagnostic ureteroscopy*
Flexible ureteroscopy is used to visualise and biopsy the ureter, renal pelvis and collecting system. Such ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [64]. Undergrading may occur from diagnostic biopsy, making intensive follow-up necessary if a kidney-sparing treatment is chosen [65]. Ureteroscopy also facilitates selective ureteral sampling for cytology to detect carcinoma *in situ* [60, 66, 67].

Flexible ureteroscopy is especially useful for diagnostic uncertainty, when 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 [66, 68].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and the diagnosis of flat lesions. Narrow-band imaging is the most promising technique to date but the results are too preliminary [68, 69]. Table 5.1 lists the recommendations for diagnosis.

5.3 Guidelines for the diagnosis of upper tract urothelial carcinomas

Recommendation	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 CT-urography for the diagnostic work-up.	A
Use diagnostic ureteroscopy and biopsy in cases where additional information will impact treatment decisions.	C
Perform retrograde ureteropyelography in case CT-urography or ureteroscopy do no reliably reveal the presence or extent of the tumour.	C

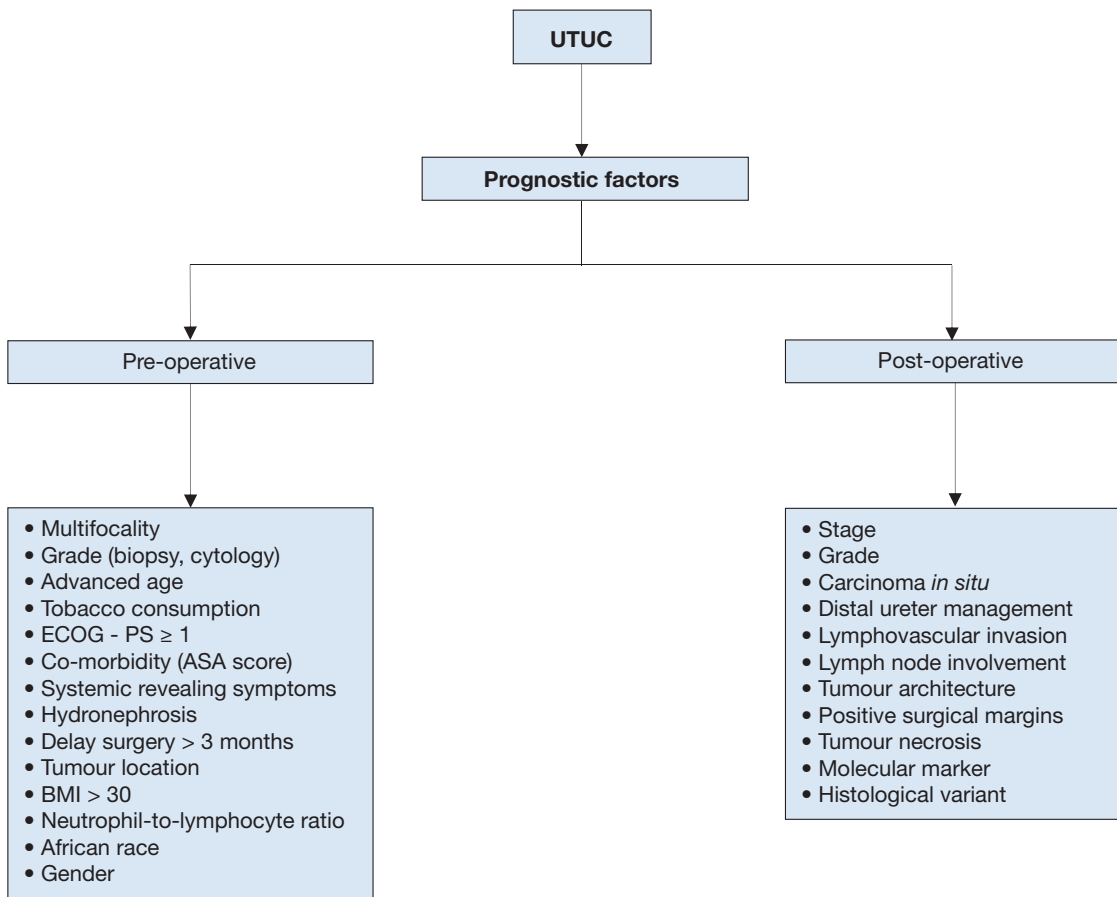*CT-urography = computed tomography urography.*

6. PROGNOSIS

6.1 Prognostic factors
Upper tract urothelial carcinomas that invade the muscle wall usually have a poor prognosis. The 5-year specific survival is < 50% for patients with pT2/pT3 tumours and < 10% for those with pT4 [69-71]. The main prognostic factors are briefly listed below; Figure 6.1 presents an exhaustive list.

Figure 6.1: Upper tract urothelial carcinoma - Prognostic factors

```
                        ┌──────────┐
                        │   UTUC   │
                        └────┬─────┘
                             │
                   ┌─────────────────────┐
                   │  Prognostic factors │
                   └──────────┬──────────┘
              ┌───────────────┴────────────────┐
    ┌──────────────────┐            ┌──────────────────┐
    │   Pre-operative  │            │  Post-operative  │
    └────────┬─────────┘            └────────┬─────────┘
             │                               │
```

Pre-operative	Post-operative
• Multifocality • Grade (biopsy, cytology) • Advanced age • Tobacco consumption • ECOG - PS ≥ 1 • Co-morbidity (ASA score) • Systemic revealing symptoms • Hydronephrosis • Delay surgery > 3 months • Tumour location • BMI > 30 • Neutrophil-to-lymphocyte ratio • African race • Gender	• Stage • Grade • Carcinoma *in situ* • Distal ureter management • Lymphovascular invasion • Lymph node involvement • Tumour architecture • Positive surgical margins • Tumour necrosis • Molecular marker • Histological variant

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

6.1.1 Preoperative factors

6.1.1.1 Age and sex
Sex is no longer considered an independent prognostic factor influencing UTUC mortality [13, 71, 72]. Older age at the time of RNU is independently associated with decreased cancer-specific survival [71, 73] (LE: 3). Many elderly patients can be cured with RNU [74], suggesting that age alone is an inadequate indicator of outcome [73, 74]. 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 [75] but population-based studies have indicated that African-American patients have worse outcomes compared to other ethnicities [74, 76] (LE: 3).

6.1.1.3 Tobacco consumption
Being a smoker at diagnosis increases the risk for disease recurrence and mortality after RNU [77, 78] as well as increases recurrence within the bladder [79] (LE: 3).

6.1.1.4 Tumour location
Initial location of the UTUC is a prognostic factor [80-82] (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 [71, 81-84].

6.1.1.5 Surgical delay
A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. The time limit from decision for RNU to its performance ranges from 30 days and 3 months [85-88] (LE: 3).

6.1.1.6   Other
The American Society of Anesthesiologists (ASA) score significantly correlates with cancer-specific survival after RNU [89] (LE: 3). The Eastern Cooperative Oncology Group (ECOG) performance status correlates only with overall survival [90]. Obesity and higher body mass index adversely affect cancer-specific outcomes in UTUCs [91, 92] (LE: 3). The pretreatment derived neutrophil-lymphocyte ratio correlates also with higher cancer-specific mortality [93, 94] (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 [66, 71, 95, 96].

6.1.2.2   Lymph node involvement
Extranodal extension is a powerful predictor of clinical outcomes in UTUCs and positive lymph node metastases [97]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging [98, 99] (LE: 3). Lymph node invasion is an important prognostic factor, indicating metastatic spread to the lymph nodes.

6.1.2.3   Lymphovascular invasion
Lymphovascular invasion is present in ~20% of UTUCs and is an independent predictor of survival [100, 101]. Lymphovascular invasion status should be specifically reported in the pathological reports of all RNU specimens [100, 102] (LE: 3).

6.1.2.4   Surgical margins
Positive soft tissue surgical margin after RNU is a significant factor for developing UTUC metastases. Pathologists should look for, and report, positive margins at the level of ureteral transection, bladder cuff, and around the tumour soft tissue margin [103] (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 [104, 105] (LE: 3). The tissue architecture of UTUC is also a strong prognosticator with sessile growth pattern being associated with worse outcome [106, 107] (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 [108-110] (LE: 3). Similar to lower tract UC, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease [111].

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-1α 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 [71, 112-117]. Microsatellite instability (MSI) is an independent molecular prognostic marker [118] and can help detect germline mutations and hereditary cancers [15].

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 preoperative 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].
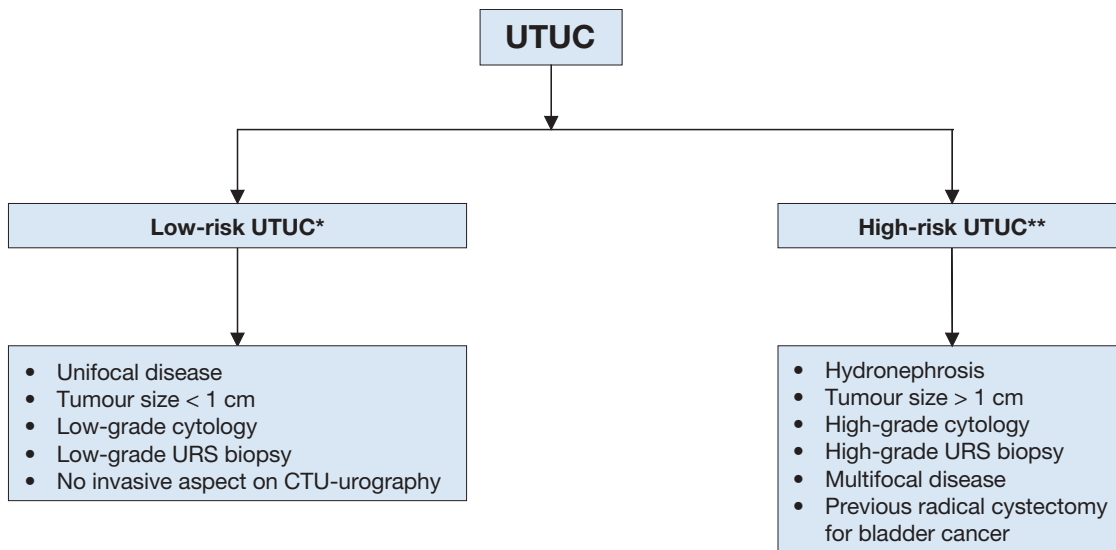
6.4   Bladder recurrence
A recent meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [8] (LE: 3). Three categories of predictors of increased risk for bladder recurrence were identified:
•   patient-specific factors such as (male gender, previous bladder cancer, preoperative chronic kidney disease);
•   tumour-specific factors such as (positive preoperative urinary cytology, ureteral location, multifocality, invasive pT stage, necrosis);
•   treatment-specific factors such as (laparoscopic approach, extravesical bladder cuff removal, positive surgical margins) [8].

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 carcinomas

```
                              UTUC
                                |
            ┌───────────────────┴───────────────────┐
            ↓                                        ↓
      Low-risk UTUC*                          High-risk UTUC**
            |                                        |
            ↓                                        ↓
  • Unifocal disease                      • Hydronephrosis
  • Tumour size < 1 cm                    • Tumour size > 1 cm
  • Low-grade cytology                    • High-grade cytology
  • Low-grade URS biopsy                  • High-grade URS biopsy
  • No invasive aspect on                 • Multifocal disease
    CTU-urography                         • Previous radical cystectomy
                                            for bladder cancer
```

*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 lymphocascular invasion.	3

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

MSI = Microsatellite instability.

7. DISEASE MANAGEMENT

7.1 Localised disease

7.1.1 Kidney-sparing surgery

Kidney-sparing surgery 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. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney [129-131].

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 patient 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 understaging and undergrading remains with endoscopic management.

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-risk UTUCs in the renal cavities [133, 136, 137] (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. This approach is being used less due to the availability of improved materials and advances in distal-tip deflection of recent ureteroscopes [133, 136, 137].

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 [138-140] (LE: 3).
- Segmental resection of the iliac and lumbar ureter is associated with higher failure rates than for the distal pelvic ureter [138-140] (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
In patients with solitary kidney and/or impaired renal function, offer kidney-sparing management, 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
In high-risk cancers, offer a kidney-sparing approach for distal ureteral tumours and in imperative cases (solitary kidney and/or impaired renal function).	C
Offer kidney-sparing management in case of:	
• Unifocal tumour; • Tumour < 1 cm; • Low-grade tumour; • No evidence of infiltrative lesion on CTU; • Understanding of close follow-up.	B
If treatment is done endoscopically, use a laser.	C

CTU = computed tomography urography.

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 [141] (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 [142].

7.1.2 **Radical nephroureterectomy**

Open RNU with bladder cuff excision is the standard treatment for high-risk UTUC, regardless of tumour location [12] (LE: 3). Radical nephroureterectomy must comply with oncological principles, that is preventing tumour seeding by avoidance of entry into the urinary tract during resection [12].

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 [129, 138, 143].

       Several techniques have been considered to simplify distal ureter resection, including pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception [9, 143, 144]. Except for ureteral stripping, none of these techniques is inferior to bladder cuff excision [73-75, 81] (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 [145, 146].

Several precautions may lower the risk of tumour spillage:
- Avoidance to enter the urinary tract;
- Avoidance of direct contact between instruments and the tumour;
- Laparoscopic RNU must take place in a closed system. Avoidance of morcellation of the tumour and an endobag for tumour extraction should be used;
- 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 [146-152] (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 [153] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and refinements in staging and surgical technique [154] (LE: 3). A robot-assisted laparoscopic approach can be can be considered, but solid data are still lacking [155].

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 [97]. An increase in the probability of lymph-node-positive disease is related to pT classification [99]. 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 [156, 157]. LND can be achieved following lymphatic drainage as follows: LND medial to the ureter in ureteropelvic tumour, 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) [96, 97, 129].

7.1.2.3 Adjuvant bladder instillation

The rate of bladder recurrence after RNU for UTUC is 22-47% [8, 158]. 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 [159-161] (LE: 1b).

7.1.2.4   Guidelines for radical nephroureterectomy

Recommendations	GR
RNU is the standard in high-risk UTUC, regardless of tumour location.	B
Use RNU in the following situations:	
• Suspicion of infiltrating UTUC on imaging;	B
• High-grade tumour (urinary cytology);	B
• Multifocality (with two functional kidneys);	B
• Non-invasive but large (> 1 cm) UTUC.	B
RNU techniques:	
• Remove the bladder cuff;	A
• Perform a lymphadenectomy in invasive UTUC;	C
• Offer a post-operative bladder instillation to lower the bladder recurrence rate.	B
Open and laparoscopic approaches have equivalent efficacy and safety in T1–T2/N0 UTUCs.	B

RNU = radical nephroureterectomy.

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
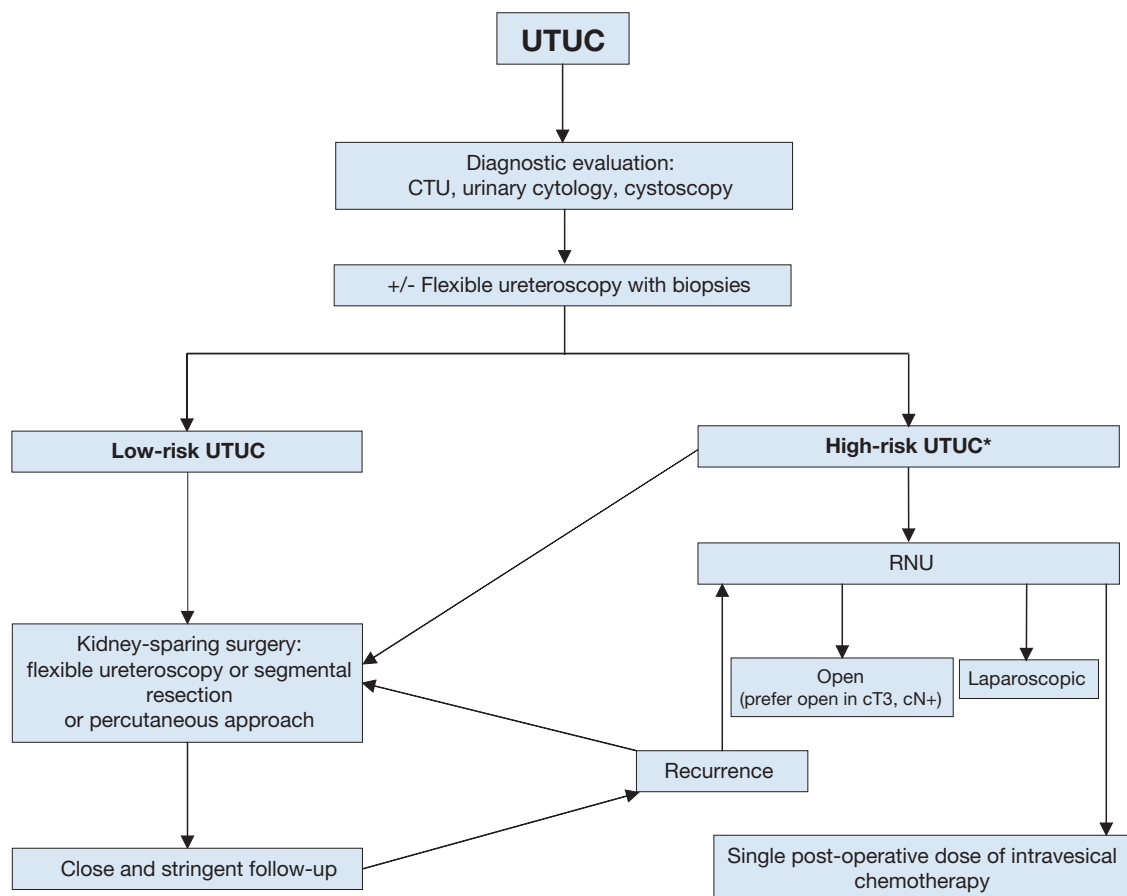
CTU = computed tomography urography; RNU = radical nephroureterectomy.
*In patients with a solitary kidney, consider a more conservative approach.

Figure 7.2: Surgical treatment according to location and risk status
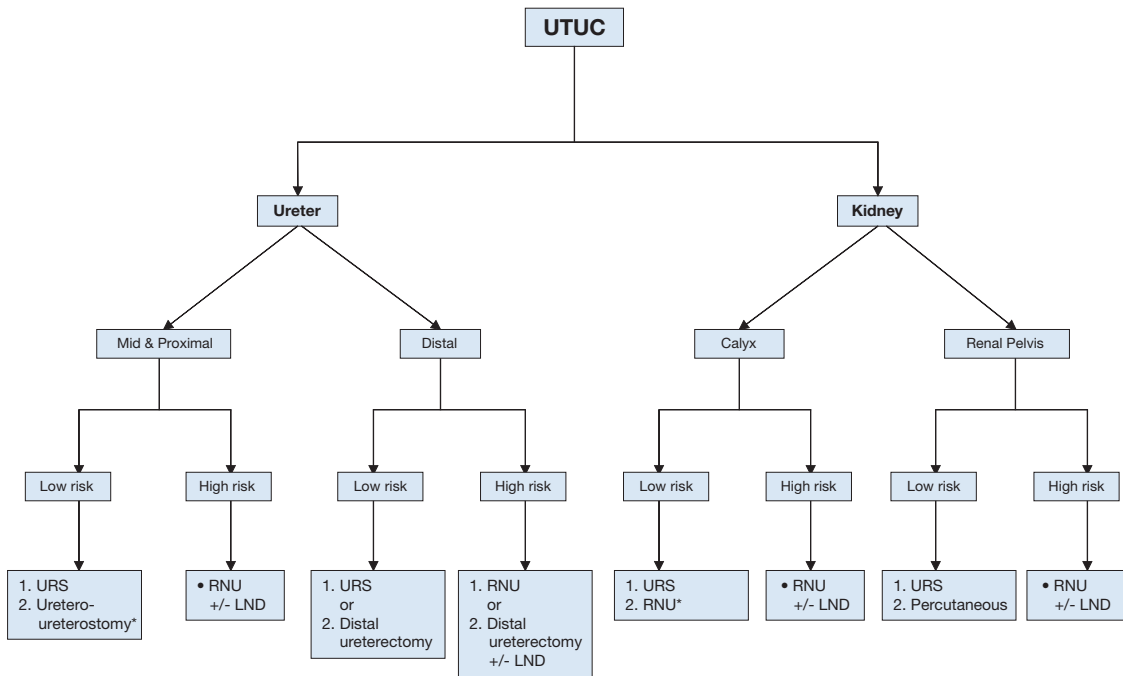
1. First treatment option
2. Secondary treatment option
In case not amendable to endoscopic management.

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 [12, 99] (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 to base recommendations on.

There are several platinum-based regimens [162], 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 [163, 164].

There were no adverse effects of neoadjuvant chemotherapy for UTUCs in the only study published to date [165], although survival data need to mature and longer follow-up is awaited. Adjuvant chemotherapy can achieve a recurrence-free rate of ≤ 50% [166, 167].

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 [168] (LE: 3). However, there are currently insufficient data to base recommendations on until further evidence from an ongoing prospective trial is available [169].

7.2.3 Radiotherapy
The role of adjuvant radiotherapy is not well defined, neither alone, nor in combination with chemotherapy [170, 171] (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.

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 RNU.	3	C

8.   FOLLOW-UP

The risk of disease recurrence and death evolves over the follow-up after surgery and is less likely with time [172, 173]. Stringent follow-up (Section 8.1) is mandatory to detect metachronous bladder tumours [9], 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 [7-9]. Bladder recurrence is not a distant recurrence [8]. When kidney-sparing surgery is performed, the ipsilateral UUT requires careful follow-up due to the high risk of disease recurrence [130, 135, 174]. Despite endourological improvements, follow-up after kidney-sparing surgery is difficult; frequent and repeated endoscopic procedures are mandatory.

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 RNU.	3

Recommendations	GR
After RNU, ≥ five years	
Non-invasive tumour	
• Perform cystoscopy/urinary cytology at three months, and then annually.	C
• Perform CT-urography every year.	C
Invasive tumour	
• Perform cystoscopy/urinary cytology at three months, and then annually.	C
• Perform CT-urography every six months for two years, and then annually.	C
After kidney-sparing management, ≥ five years	
• Perform urinary cytology and CTU at three and six months, and then annually.	C
• Perform cystoscopy, ureteroscopy and cytology *in situ* at three and six months, and then every six months for two years, and then annually.	C

CT-urography = computed tomography urography; RNU = radical nephroureterectomy.

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10.   CONFLICT OF INTEREST

EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer

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**European
Association
of Urology**

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1.1   Aims and scope
The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) has 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 (Ta,T1 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.

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-cancer-muscle-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 2014 [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 2016 document presents a limited update of the 2015 version.

1.4.2   Summary of changes
Key changes in this 2016 print:

Two new sections have been included:

- Section 7.4.3.1 - What are the oncological and functional outcomes of sexual-function preserving cystectomy compared with standard radical cystectomy in men with bladder cancer? [5].
- Section 7.4.3.2 - What are the oncological and functional outcomes of pelvic organ-preserving cystectomy compared with standard radical cystectomy in women with bladder cancer? [6].
- Section 7.4.3.3 - Laparoscopic/robotic-assisted laparoscopic cystectomy, has been completely revised.

1.4.2.1   Changes in Summary of evidence and recommendations:

3.3.3   Recommendations for the assessment of tumour specimens

Recommendations	GR
Record the number of lymph nodes and number of positive lymph nodes.	A*
Record lymphatic or blood vessel invasion.	
Record presence of CIS.	

Upgraded following panel consensus.
CIS = carcinoma in situ.

7.4.3.1.1 Summary of evidence and recommendations for sexual sparing techniques in men

Summary of evidence
The majority of patients motivated to preserve their sexual function will benefit from sexual-preserving techniques.
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: - 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 MIBC.		C

MIBC = muscle-invasive bladder cancer.

7.4.3.2.4 Summary of evidence and recommendations for sexual sparing techniques in women

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

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: • 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 MIBC.		C

MIBC = muscle-invasive bladder cancer.

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

Summary of evidence	LE
RARC has a longer operative time (1-1.5 hours), major costs; but shorter LOS (1-1.5 days) and less blood loss compared to ORC.	1
RARC series suffer from a significant stage selection bias when 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 QoL are not different between RARC and ORC.	2
Surgeons experience and institutional volume are considered the key factors 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 ORC and RARC to select 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

LOS = length of hospital stay; ORC = open radical cystectomy; QoL = quality of life; RARC = robot-assisted radical cystectomy.

2. METHODS

2.1 Data identification

For the 2016 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 April 1st 2014 until July 21st 2015. A total of 2,770 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=appendices-publications.

Two new sections of the text are based on two systematic reviews (SRs). These SRs are performed using standard Cochrane SR methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Review topics:
1. What are the oncological and functional outcomes of sexual-function preserving cystectomy compared with standard radical cystectomy in men with bladder cancer? [5].
2. What are the oncological and functional outcomes of pelvic organ-preserving cystectomy compared with standard radical cystectomy in women with bladder cancer? [6].

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://uroweb.org/guidelines/.
A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

For the 2016 publication three sections were reviewed:

- Section 7.4.3.1 - Pelvic organ preservation techniques in men: oncological and functional outcomes;
- Section 7.4.3.2 - Pelvic organ preservation techniques in women: oncological and functional outcomes;
- Section 7.4.3.3 - Laparoscopic/robotic-assisted laparoscopic cystectomy.

The remainder of the document was peer reviewed prior to publication in 2015.

2.3 Future goals

The results on ongoing and new SRs will be included in the 2017 update of the MIBC Guidelines.

Topics selected for SRs in 2017:
- Diagnostics - haematuria;
- Radical cystectomy in octogenarians.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in male population worldwide, whilst it drops to 11th when both genders are considered [8]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.0 for men and 2.2 for women [8]. In the European Union, the age-standardised incidence rate is 19.1 for men and 4.0 for women [8]. 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) [8].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.2 for men vs. 0.9 for women in 2012 [8]. BC 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 methodology used in the studies and quality of data collection [9, 10].

The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [10, 11].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, carcinoma *in situ* [CIS]) or submucosa (stage T1). They have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to T2-4 tumours [9, 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 from 1961 to 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 1-4 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. The substances involved in chemical exposure include benzene derivatives and aryl amines (2-naphthylamine, 4-ABP, 4,4'-methylenedianiline, and o-toluidine), 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 10 years or more of exposure; the mean latency period usually exceeds 30 years [18, 19]. The chemicals involved have contributed minimally to the current incidence of BC in Western countries because of strict regulations. Importantly, in recent years, the extent and pattern of occupational exposure have changed because awareness has prompted safety measures, and population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [9, 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 develop towards squamous cell carcinoma (SCC), although 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 with a total population of 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]. A population-based study from the MarketScan databases indicated that women experienced longer delays in diagnosis than men, as the differential diagnosis in women includes diseases that are more prevalent than BC [30].

Differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, postmenopausal 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 [31-33].

3.2.7 *Genetic factors*

There is growing evidence that genetic susceptibility factors and family associations may influence the incidence of BC. The relationship between family history of cancer and risk of BC was examined in a Spanish bladder cancer study. It was found 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 [34]. Recent studies detected genetic susceptibility with independent loci which are associated with BC risk [35].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [36, 37].

3.2.8 *Summary of evidence and recommendations for epidemiology and risk factors*

Summary of evidence	LE
Worldwide, bladder cancer is the 11th most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC 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

BC = bladder cancer; EBRT = external-beam radiotherapy; BT = brachytherapy; MIBC = muscle-invasive bladder cancer.

3.3 Pathology

3.3.1 Handling of transurethral resection and cystectomy specimens

In transurethral resection (TUR) specimens, the superficial and deep areas of the tumour should be 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 [38].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [39, 40]. 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 [41]. 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 specimens should be provided in their totality, in clearly labelled containers. In case of doubt, or adipous differentiation of the lymph node, the entire specimen is to be included. Lymph nodes should be counted and measured on slides, capsular effraction and percentage of lymph node invasion should be reported as well as vascular embols. In the case of metastatic spread in the perivesical fat without real lymph node structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+. The lymph node density needs to be reported.

Positive margins in the peripelvic fat tissue (soft tissue margins), should be inked by the pathologist for evaluation. Positive margins have decreased cancer-specific survival (CSS) in cases of pN0M0 urothelial carcinomas [42].

In selected cases, fresh frozen sections may be helpful to determine treatment strategy. A recent study confirmed the reliability of fresh frozen sections of obturator lymph nodes, but similar studies are warranted to confirm these results [43].

3.3.2 Pathology of muscle-invasive bladder cancer

In MIBC there are usually no cases of papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade carcinoma. All cases are high-grade urothelial carcinomas. For this reason, no prognostic information can be provided by grading muscle-invasive BC [44]. However, some morphological subtypes can be important in helping with prognosis and treatment decisions [45, 46]. Recently an update of the World Health Organization (WHO) grading was published [47] but the data presented in these guidelines are based on the 2004 WHO classification [48]. Currently the following differentiation is used:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular differentiation [49, 50];
3. micropapillary and microcystic urothelial carcinoma;
4. nested variant [51] (including large nested variety); lymphoepithelioma, plasmocytoid, giant cell, undifferentiated;
5. some urothelial carcinomas with trophoblastic differentiation;
6. small-cell carcinomas [52];
7. sarcomatoid carcinomas.

3.3.3 ***Recommendations for the assessment of tumour specimens***

Recommendations	GR
Record the depth of invasion (categories pT2a & pT2b, pT3a, pT3b or pT4).	A*
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 and number of positive lymph nodes.	
Record lymphatic or blood vessel invasion.	
Record the presence of CIS.	

Upgraded following panel consensus.
CIS = carcinoma in situ.

4.   STAGING AND CLASSIFICATION SYSTEMS

4.1   Pathological staging

For staging, the TNM classification (2009, 7th edition) is recommended [53]. Blood and lymphatic vessel invasion and lymph node infiltration have an independent prognostic significance [54]. It seems that the pN category is closely related to the number of lymph nodes studied by the pathologist [55].

New prognostic markers are under study (see Section 6.2.4 Prognostic Markers).

4.2   Tumour, node, metastasis classification

The tumour, node, metastasis (TNM) classification of malignant tumours is the method most widely used to classify the extent of cancer spread. A seventh edition was published, effective as of 2010 [45, 46, 53] (Table 4.1).

Table 4.1: TNM classification of urinary bladder cancer [53]

T - Primary Tumour		
Tx	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: "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 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	
M1	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 [56, 57]. 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 [58].

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.

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% [59, 60] (LE: 2b). However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [61].

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 [62].

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 include 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 [63].

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 [64, 65] (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 [66-68].

5.1.7   ***Second resection***
In the case of high-grade non-muscle-infiltrative tumour, residual disease is observed in 33-53% of patients [69-75]. In order to reduce the risk of understaging [70, 71], 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 cysto-prostatectomy 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 [76, 77]. 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
Cystoscopy should 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 CIS 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.	
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

CIS = carcinoma in situ.

5.2   Imaging for staging of MIBC
The treatment and prognosis of MIBC is determined by tumour stage and grade [78, 79]. 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 lymph nodes;
•   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) [80]. 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 [81]. Dynamic contrast-enhanced (DCE) MRI may help to differentiate bladder tumour from surrounding tissues or post-biopsy reaction, because enhancement of the tumour occurs earlier than that of the normal bladder wall, due to neovascularisation [82-84].

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 [85] (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% [86] and increases with more advanced disease [87].

5.2.2 Imaging of lymph nodes in MIBC
Assessment of lymph node 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 lymph node 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 lymph node metastases in a variety of primary pelvic tumours [88-93]. 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 [94, 95].

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 [96-99].

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 [100]. 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 [101-108]. 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 [102, 103, 109-111]. 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 [112] and liver metastases [113], 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 [114, 115]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [116, 117] (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 [118, 119], 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 [120]. 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 MIBC

Summary of evidence	LE
Imaging as part of staging in MIBC provides information about prognosis and assists in selection of the most appropriate treatment.	2b
There are currently insufficient data on the use of DWI and FDG-PET/CT in MIBC to allow a recommendation to be made.	

Recommendations	GR
In patients with confirmed MIBC, use 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 UTUC using excretory-phase CT urography rather than 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 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

CT = computed tomography; DWI = diffusion-weighted imaging; FDG-PET/CT = fluorodeoxyglucose-positron emission tomography; MIBC = muscle-invasive bladder cancer; MRI = magnetic resonance imaging; UTUC = upper urinary tract urothelial carcinoma.

6.   PROGNOSIS

6.1   Introduction
The treatment and prognosis for MIBC is determined by tumour and nodal stage [79]. 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 [121-123].

Advanced age has been identified as a risk factor for complications in the case 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 [124]. Female gender, an increased body mass index and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [125].

Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal complications and a decrease of recurrence free- and overall survival (OS) after RC [126, 127]. 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 [128]. 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 [129].

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 [130]. 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 [131]. 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 [132]. 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 [133]; six of which have been validated [134-139] (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 [140, 141], overall mortality [142], and cancer-specific mortality [143-146]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [147]. 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 [148].

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
1. Calculate Charlson 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
3. Calculate Charlson Probability (10-year mortality)
a. Calculate $Y = 10^{(i \times 0.9)}$
b. Calculate $Z = 0.983^Y$ (where Z is the 10-year survival)

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 [149]. The Eastern Cooperative Oncology Group (ECOG) PS scores and Karnofsky index have been validated to measure patient activity [150] (LE: 3). Performance score is correlated with patient OS after RC [145, 151] and palliative chemotherapy [152-154].

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) [155] which is tailored to the care of cancer patients [156]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated elderly patients with advanced BC [157].

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 BC would be helpful.	3

Recommendations	GR
Base the decision on bladder-sparing 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 ASA score should not be used in this setting (see section 7.4.4.1).	

ASA = American Society of Anesthesiologists; BC = bladder cancer.

6.2.4 **Prognostic markers**
Currently, insufficient evidence exists to recommend the standard use of the 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.

Recent publications could demonstrate four molecular groups of bladder cancer:
• Basal BC with the basal and claudin low-type group, and
• luminal bladder cancer 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), ERBB3, epidermal growth factor receptor (ERBB2↑), and is chemotherapy resistant [45, 46, 158].

Tumour location may also be a useful prognostic factor. 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 a decreased survical OR 1.68 (95% CI: 1.11-2.55) [78].

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 [159]. According to this calculator, the risk of progression after 5 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 5 years was much lower: 19.3% for T1G3 tumours [160].
Meta-analyses have demonstrated that BCG-therapy prevents the risk of tumour recurrence [161] and the risk of tumour progression [162, 163] but so far, no significant overall- or disease-specific survival advantages have been shown, as compared to no intravesical therapy [162-164]. 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 [165-167]. Second TURB identifies upstaging to > T2 tumours in 10-20% [168, 169].
        Progression to MIBC significantly decreases CSS. In a review of 19 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, 170, 171].

According to the EAU NMIBC Guidelines, it is reasonable to propose immediate RC to those patients with non-

muscle-invasive tumour who are at highest risk of progression [159, 172-174]. These 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 largeT1G3/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 10-year recurrence-free survival rate is 80% and similar to that with TURB and BCG maintenance therapy [2, 166, 175, 176] (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 3 months;
* if CIS (without concomitant papillary tumour) is present at both 3 and 6 months;
* If high-grade tumour appears during BCG therapy [177];
* 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 2 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 [178] (LE: 3; GR: C).

There are now several bladder-preservation strategies available; immunotherapy, chemotherapy, device-assisted therapy, and combination therapy [179]. However, experience is limited and treatments other than RC must be considered oncologically inferior at the present time [179].

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, CIS, and tumour size, as outlined in the EAU guidelines for non-muscle-invasive bladder cancer [2]).	C
Offer radical treatment to all T1 patients failing intravesical therapy.	B

CIS = carcinoma in situ; EAU = European Association of Urology.

7.2   Neoadjuvant chemotherapy
7.2.1   Introduction
The standard treatment for patients with MIBC is RC. However, this gold standard only provides 5-year survival in about 50% of patients [167, 180-183]. To improve these unsatisfactory results, neoadjuvant chemotherapy (NAC) has been used since the 1980s [184, 185].

There are many advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with operable muscle-invasive urothelial carcinoma of the bladder and cN0M0 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 [186,

187], although published studies on the negative effect of delayed cystectomy only include chemo-naive 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 [188]. 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 [189].
- Clinical staging using bimanual palpation, CT or MRI may often result in over- and understaging and have a staging accuracy of only 70% [190, 191]. Overtreatment is a possible negative consequence.
- NAC 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 [188, 192-204].

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 [205-208]. 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 [209]. 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 tumour molecular profiling in TURB specimens might guide the use of NAC [210, 211] (see Section 7.8.11 - Biomarkers).

7.2.3 *Summary of available data*
Several randomised phase III trials addressed the potential survival benefit of NAC administration, with conflicting results [188, 192-201, 212-217]. 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 answer the question whether NAC prolongs survival, or not [202-204]. In the most recent meta-analysis, published in 2005 [204], with updated patient data from 11 randomised trials (3,005 patients), 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 5 years.

The Nordic combined trial showed an absolute benefit of 8% survival at 5 years and 11% in the clinical T3 subgroup, translating into nine patients needed to treat [189]. Only cisplatin combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [202, 204]; 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 CarboMV.

More modern chemotherapeutic regimens such as gemcitabine/cisplatin have shown similar pT0/pT1 rates as MVAC in the most recent retrospective series and pooled data analyses, but have not been used in randomised controlled trials (RCTs) [218-221]. The updated analysis of the largest randomised phase III trial [192] with a median follow-up of 8 years confirmed previous results and provided some additional interesting findings:
- 16% reduction in mortality risk;
- Improvement in 10-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 [189]. Further data support the use of NAC in the T2b-T3b tumour subgroup (former classification T3), which has shown to provide a modest, but substantial, improvement in long-term survival as well as significant downstaging [209].

7.2.4   *Summary of evidence and recommendations for neoadjuvant chemotherapy*

Summary of evidence	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 OS (5-8% at 5 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. In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for neoadjuvant chemotherapy and differentiate responders from non-responders.	

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

OS = overall survival.

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, reducing the damage to surrounding tissue, may yield better results in the future [222]. A recent RCT in 100 patients, comparing pre-operative vs. post-operative RT and RC, showed comparable OS, DFS and complication rates [223]. Approximately half of these patients had 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 [224].

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 [225]. A more recent retrospective study compared the long-term outcome of pre-operative vs. no pre-operative RT in clinical T1-3 tumours [226]. Downstaging to T0 after cystectomy occurred in 7% (7/97) without RT vs. 57% (51/90) with RT. In cT3 tumours, these results were 0% (0/16) vs. 59% (19/34), respectively. 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 [227]. 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 not included in the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in ≥ T3 tumours [228, 229]. Two other small trials confirmed downstaging after pre-operative RT [230, 231].
        A meta-analysis of the five randomised trials showed an OR for the difference in 5-year survival of 0.71 (95% CI: 0.48-1.06) in favour of pre-operative RT [232]. However, the meta-analysis was potentially biased by the patients in the 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 for operable MIBC increases survival.	2a
Pre-operative radiotherapy for operable MIBC, using a dose of 45-50 Gy in fractions of 1.8-2 Gy, results in downstaging after 4-6 weeks.	2
Limited high-quality evidence supports the use of pre-operative radiotherapy to decrease the local recurrence of MIBC after radical cystectomy.	3

Recommendations	GR
Do not offer pre-operative radiotherapy to improve survival.	A
Offer pre-operative radiotherapy for operable MIBC since it can result in tumour downstaging after 4-6 weeks.	C

MIBC = muscle-invasive bladder cancer.

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 [167, 233]. 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 [143]. The analysis found an association between comorbidity and adverse pathological- and survival outcome following RC [143]. Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [149].

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 [143]. 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 [234].

It is particularly important to evaluate the function and QoL of elderly patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation (see Section 6.2) [235].

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 [236]. Ayres *et al.* investigated whether a delay > 3 months would have the same effect in the United Kingdom [237]. 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 12 weeks has a negative impact on outcome and should be avoided [238].

7.4.2.1 Indications

Traditionally, RC was recommended for patients with MIBC T2-T4a, N0-Nx, M0 [233]. 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 chemo- 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 lymph nodes, 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 [239].

7.4.3 Radical cystectomy: technique and extent

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional lymph nodes. 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 [240]. In women, standard RC includes removal of the bladder, entire urethra and adjacent vagina, uterus, distal ureters, and regional lymph nodes [241]. 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 investigations for RC have been performed so far. The first investigation 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 lymph nodes. 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 [242]. The second autopsy investigation focused on the nodal yield when super-extended pelvic lymph node dissection (LND) was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [243]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional lymph nodes have been shown to consist of all pelvic lymph nodes below the bifurcation of the aorta [244-248]. Mapping studies have also found that skipping lesions at locations above the bifurcation of the aorta, without more distally located lymph node metastases, is rare [248, 249].

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 [250]. Extended lymphadenectomy includes all lymph nodes 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 lymph node of Cloquet, as well as the area described for standard lymphadenectomy [250-254]. A super-extended lymphadenectomy extends cranially to the level of the inferior mesenteric artery [255, 256].

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 [257]. Out of 1,692 abstracts retrieved and assessed, 19 studies fulfilled the review criteria [250-254, 256, 258-270]. All five studies comparing LND vs. no LND reported a better oncological outcome for the former group. Seven out of 12 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-analysis [271, 272]. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [256, 268]. Further data from on-going randomised trials on the therapeutic impact of the extent of lymphadenectomy are awaited.

It has been suggested that progression-free survival as well as OS might be correlated with the number of lymph nodes removed during surgery, although there are no data from RCTs on the minimum number of lymph nodes that should be removed. Nevertheless, survival rates increase with the number of dissected lymph nodes [273]. Removal of at least 10 lymph nodes has been postulated as sufficient for evaluation of lymph node status, as well as being beneficial for OS in retrospective studies [274-276]. In conclusion, extended LND might have a therapeutic benefit compared to less-extensive LND, but due to bias, no firm conclusions can be drawn [257].

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 [5].

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, 12 full-text articles were included (Table 7.1).

Table 7.1: Pelvic organ-preserving cystectomy series in men

Study ID	Type of surgery	Number of patients Entire study	Intervention	Control	Type of study		Country	Recruitment period
De Vries et al. 2009/ Mertens et al. 2014 [240, 277]	Prostate sparing vs. RC	126	63	63	Comparative	Retrospective (Matched pair)	Netherlands	1994-2006
Gotsadze et al. 2008 [278]	Prostate sparing	87	87		Non-comparative	Retrospective	Georgia	1991-2005
Basiri et al. 2012 [279]		50	23	27	Comparative	Retrospective (Matched pair)	Iran	2003-2008
Wang et al. 2008 [280]	Capsule sparing vs. RC	36	27	9	Comparative	Retrospective	China	2000-2006
Moon et al. 2005 [281]		35	17	18	Comparative	Retrospective	Korea	1999-2003
Rozet et al. 2008 [282]		108	108		Non-comparative	Retrospective	France	1992-2004
Muto et al. 2014 [283]	Capsule sparing	91	91		Non-comparative	Retrospective	Italy	1990-2009
Vilaseca et al. 2013 [284]		44	11	33	Comparative	Retrospective	Spain	2006-2009
El-Bahnasawy et al. 2006 /Hekal 2009 [285, 286]	Nerve sparing vs. RC	60	30	30	Comparative	Retrospective	Egypt	2003-2005
Kessler et al. 2004 [287]		331	256	75	Comparative	Retrospective	Switzerland	1985-2003
Intervention vs. Intervention								
Jacobs et al. 2015 (RCT) [288]	Capsule sparing vs. Nerve sparing	40	20	20	RCT	Prospective	USA	2007-2011
Colombo et al. 2015 [289]	Capsule sparing vs. Seminal sparing vs. Nerve sparing	90	CS:36 SS:19 NS:35		Comparative	Retrospective	Italy	1997-2012

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 3 to 5 years. Local recurrence after SPC was commonly defined as any urothelial cancer 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% (vs. 33%).

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 8 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 PSC patients. No major impact was shown with regard to continence rates for any of the three approaches.

7.4.3.1.1   Summary of evidence and recommendations for sexual sparing 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: - 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 MIBC.		C

MIBC = muscle-invasive bladder cancer.

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

7.4.3.2.1   Introduction

Sexual and voiding dysfunction is prevalent after RC. 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 for female patients [6].

7.4.3.2.2   Oncological outcomes

After screening 9,263 abstracts, 14 studies were selected, reporting functional or oncological outcomes (Table 7.2). 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.

From all patients enrolled: 93 (29.2%) had ≥ pT3 disease and 48 (15%) had positive lymph nodes. Carcinoma *in situ* was found in 23 (7%) bladder specimens. Positive surgical margins were reported in 6 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 7 months. Survival outcomes of 318 cumulative patients with a mean follow-up between 12 and 132 months was reported. At 3 and 5 years, CSS was 70-100% and OS was 65-100%.

Table 7.2: Pathological characteristics and oncological outcomes of patients with preserving technique

Reference	No of patients with preserving technique	Follow-up (Mo, mean)	Pathologic bladder stage ≥ T3 (n)	Extension of LND	Pathologically node positive disease (n)	Pathological CIS (n)	Positive surgical margins (n,%)	Local recurrence (n)	Time to local recurrence (median, range, Mo)	Metastatic recurrence (n)	Deaths to bladder cancer (n)	DSS (%)	OS (%)
Vaginal-sparing RC													
Large et al. 2012 [290]	94	27,7	42 (44.7%)	NR	25 (26,6%)	NR	8 (8,5%)	11 (11.7%)	NR	NR	NR	NR	NR
Chang et al. 2002 [291]	21	12 (1-36)	4 (19%)	Pelvic	1 (5%)	3 (14%)	1 (5%)	1 (5%)	6	2 (9.5%)	2 (9.5%)	NR	NR
Granberg et al. 2008 [292]	53	29.2 (1-141)	T3 18 (34%); T4 1 (2%)	Pelvic	11 (21%)	7 (13%)	1/53 (2%)	7 (13%)	8 (2-36)	8 (15%)	2 (8%)	5yr 88%	5 yr 83%
Neymeyer et al. 2009 [293]	86	36	NR	Pelvic	NR	NR	NR	NR	NR	NR	NR	NR	NR
Anderson et al. 2012 [294]	49	37.2 ± 37.2	T3 12	Pelvic	2 (3.9%)	10 (19.6%)	7 (13.7%)	NR	NR	NR	NR	NR	NR
Rouanne et al. 2014 [295]	46	68 (6-204)	pT3 13 (42%)	Pelvic	3 (10%)	NR	NR	NR	NR	NR	NR	NR	5 yr 79%
Gross et al. 2015 [296]	73	64 (12-227)	pT3 21 (28.8); pT4 3(4)	Pelvic	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nerve-sparing RC													
Nesrallah et al. 2005 [297]	29	37.5 (14-96)	NR	Pelvic	2 (7%)	NR	NR	NR	NR	7 (24%)	2 (7%)	3 yr 76%	3 yr 65%
Bhatt et al. 2006 [298]	6	13.2 (12-14)	0	Pelvic	0	NR	NR	NR	NR	0	0	NR	NR
Genital-sparing RC													
Ali-El-Dein et al. 2013 [299]	15	72 (37-99)	15 (100%)	Iliac	1 (6,7%)	NR	NR	1 (6.7%)	NR	2 (13%)	3 (20%)	5 yr 80%	5 yr 80%
Horenblas et al. 2001 [300]	3	42 (24-72)	1 (7.7%)	Pelvic	0	1 (7.7%)	NR	0	NR	0	0	NR	NR
Koie 2010 [301]	30	41 (4-98)	10 (33.3%)	Pelvic	NR	NR	0%	1 (3.3%)	<7	5 (16.7%)	9 (30%)	5 yr 70%	NR
Kulkarni et al. 2008 [302]	14	24.5 (12-65)	-	Pelvic	5 (36%)	NR	NR	1 (7%)	NR	1 (7%)	2 (14%)	NR	NR
Wishahi et al. 2015 [303]	13	132 (60-180)	pT3a 3 (23%)	iliac	0	0	0%	NR	NR	NR	NR	5 yr 100%; 10 yr 62%	5 yr 100%; 10 yr 62%

7.4.3.2.3   Functional outcomes
Sexuality after orthotopic diversion and pelvic organ-preserving cystectomy
Nine studies (n = 280) reported continence outcomes of patients with pelvic organ-preserving cystectomy. Overall day-time and night-time continence was 70.3% and 67.2%, respectively. The self-catheterisation rate was 17.6%. Continence outcome assessment and measurement was heterogeneous. Some studies used objective measures such as the number of PADs used daily, whereas others used patient reported outcomes. Nevertheless, definition of complete continence was common for all nine studies, regardless of assessment modalities, consisting of complete dryness.

Table 7.3 presents the data from pelvic organ-preserving cystectomy series in women reporting sexual function outcomes. Six studies, including 150 patients, were considered for the analyses. At the time of surgery, mean patient age ranged from 37.9 to 64.8 years. Mean duration of post-operative follow-up ranged between 13.2 and 132 months. Sexual function outcomes were evaluated at least 6 months after surgery.

However, in the majority of studies evaluation of baseline sexual function is lacking. Only Bhatt *et al.* [298] collected data at baseline and post-operatively. Interestingly, they found a minimal decline in mean Female Sexual Function Index (FSFI) scores from 24.5 to 22.3, in the nerve-sparing group (mean age 55.9 years). However, no comparative data are available. Additionnally, no significant decline or difference was observed when analysing each of the six domains evaluated by the FSFI questionnaire separately.

Overall, 130/150 patients (86.7%) had resumed sexual activity at the date of analysis. Satisfaction related to patients' sexuality was mentioned in 4 out of 6 studies and the reported rates ranged from 80% to 100%. Only one study reported a post-operative delay of 6 weeks to restart sexual activity. The definition of sexual activity included either sexual intercourse and/or vaginal manipulation.

Four studies used validated standardised questionnaires to assess sexual function (i.e. the Female Sexual Function Index [FSFI] and the Contilife), two of which were based on a physician interview. When FSFI was used, final (mean) score ranged from 18/36 to 23.7/36. Only two small studies retrospectively compared nerve-sparing techniques to a non-nerve-sparing control group [298, 299]. Both studies found a better preserved FSFI score in the nerve-sparing group.

Table 7.3: Pelvic organ-preserving cystectomy series in women reporting on sexual outcomes

References	No. pts assessed	Age, yr (mean, range)	Type of diversion	Mean duration of follow-up	Baseline evaluation	Measure	Sexual activity	Satisfaction	FSFI score (mean)
Neymeyer J *et al.* 2009 [293]	86	NR	Neobladder	36 mo (6-54)	No	Interview	89.5%	95.3%	NR
Ali-el-Dein B *et al.* 2013 [299]	12/15	42 (25-54)	Hautmann neobladder	70 mo (37-99)	No	FSFI	100%	100%	18
Horenblas S *et al.* 2001 [300]	2/3	55 (38-71)	Neobladder	42 mo (24-72)	No	Interview	NR	100%	NR
Bhatt A *et al.* 2006 [298]	6/13	55.9 (52-59)	Neobladder	13.2 mo (12-14)	Yes	FSFI	100%	80%	22.3
Rouanne M *et al.* 2014 [295]	31/46	64.8 (43-86)	Z-shaped neobladder	68 mo (6-204)	No	Contilife	58%	NR	NR
Wishahi M *et al.* 2015 [303]	13/13	37.9 (20-54)	U-shaped neobladder	132 mo (60-180)	No	FSFI	92.3%	NR	23.7

7.4.3.2.4   Summary of evidence and recommendations for sexual sparing techniques in women

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

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: • 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 MIBC.		C

MIBC = muscle-invasive bladder cancer.

7.4.3.3   Laparoscopic/robotic-assisted laparoscopic cystectomy
Due to data limitations, 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 [304], a consensus panel report [305], a RCT from the Memorial Sloan Kettering Cancer Center (MSKCC) group [306], a SR on oncologic and functional outcomes after RARC [307], and a retrospective review on the recurrence patterns after ORC and RARC [308]. Since there is a continuous flow of reports on RARC, this text section and the recommendations will be be subject to significant updates in the coming years.
For the methodology of the SR we refer to the manuscript [304]. In short, out of 1,071 abstracts assessed, 105 studies were selected as meeting the prespecified inclusion criteria. Of the 105 papers 102 had a LE 4, and only three publications had a LE 2b. Several items were studied in detail.
For RARC with urinary diversion, the mean operative time was 6 to 7 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 (LOS) for RARC decreases with time and experience, and seems 1 to 1.5 days shorter compared to ORC. In the RCT's however, operative time and LOS showed no significant difference for either procedure. Blood loss and transfusion rate favour RARC. Intra-operative, 30-day complications and 30-day 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 [306], compared to a large series of ORC (n = 1,054) [167] 47% of included patients had a < pT2 tumour.

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 [305]. They presented similar outcomes comparing RARC and ORC for operative endpoints, pathological and intermediate oncological endpoint (positive surgical margins (PSM's) and lymph node yield), functional endpoints and complication outcomes. Additionally, RARC resulted in increased costs, although there are ergonomic advantages for the surgeon, as compared to 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 a 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 or 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 RARC's/year and experience in open cystectomy.

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 [306]. Since the complication rates were similar (62% for RARC vs. 66% for ORC), the trial was closed after a planned interim analysis. RARC resulted in less blood loss but had a longer operative time 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 [309]. Similar functional and oncological outcomes with 5 years follow up were also reported by Yuh *et al.* [307]. Ngyuyen *et al.* also reported that RARC was not an independent predictor of recurrence after surgery in a retrospective review of 383 consecutive patients [308].

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

Although an intracorporeal neobladder is a very complex robotic procedure [310] the choice for neobladder or cutaneous diversion, not the shape and functional results of the neobladder, must not depend on the surgical approach.

For LRC, a recent review came to similar conclusions as described above for RARC [310]. The review included 16 eligible studies and LRC, as compared to ORC, had a significantly longer operative time, fewer overall complications, blood transfusions and analgesic use, less blood loss and a shorter LOS. 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 [310].

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

Summary of evidence	LE
RARC provides longer operative time time (1-1.5 hours), major costs; but shorter LOS (1-1.5 days) and less blood loss compared to 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 QoL 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 patients of advantages and disadvantages of ORC and RARC to select 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

LOS = length of hospital stay; ORC = open radical cystectomy; QoL = quality of life; RARC = robot-assisted radical cystectomy.

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 [311]. 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 [126, 312], particularly those related to the type of urinary diversion (Table 7.4) [313]. However, the ASA score is not a comorbidity scale and should not be used as such.

Table 7.4: ASA score [314]

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 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 cysto-prostatectomy specimen just under the verumontanum and on the inferior limits of the bladder neck for females.

When there are positive lymph nodes, 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 [315].

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 [316].

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 [317]. Despite the necessary interruption and re-anastomosis of bowel, a formal bowel preparation may not be necessary [318]. Furthermore, bowel recovery time has been reduced by the use of early mobilisation and early oralisation, gastrointestinal stimulation with metoclopramide and chewing gum [319]. 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, suffer less from wound healing disorders, fever, thrombosis and pain [320].

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 [321]. 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 [322].

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 [323]. Age alone is not a criterion for offering continent diversion [322, 324]. 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 [325-328]. Nevertheless, no RCTs comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

7.4.4.2.1   Ureterocutaneostomy
Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. It is considered a safe procedure. It is therefore preferred in older, or otherwise compromised, patients, who need a supravesical diversion [329, 330]. 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 [234].

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 [329].

In a retrospective comparison with short or median follow-up of 16 months, the diversion-related complication rate was considerably lower for ureterocutaneostomy compared to ileal or colon conduit [331]. 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 [332].

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 [332]. 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% [333-335]. 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) [333]: 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 [336-338]. Different anti-reflux techniques can be used [241]. Most patients have a well-functioning reservoir with day-time and night-time continence approaching 93% [339]. 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 [339]. Stone formation in the pouch occurred in 10% of patients [339-341]. In a small series of previously irradiated female patients, incontinence and stomal stenosis was seen in 8/44 patients (18%) [342].

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) [343, 344]. 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 [315, 316]. 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 [345].

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 [180, 233, 322]. In elderly patients (> 80 years), however, it is rarely performed, even in high-volume expert centres [346, 347]. 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 [233]. 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 [348, 349]. In two studies with 1,054 and 1,300 patients [322, 350], 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 [351]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [322, 352]. 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 [353-355].

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, 349]. 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 lymph nodes (extent undefined) (LE: 2b). In female patients, standard RC includes removal of the entire bladder, urethra and adjacent vagina, uterus, distal ureters, and corresponding lymph nodes.

A detailed investigation of the bladder neck prior to RC is important for women who are scheduled for an orthotopic bladder substitute [356]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12-16% [357]. 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 [358].

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 [359, 360]. In selected patients, f.i. 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 [180, 323, 325, 361, 362]. In a large single-centre series, early complications (within three months of surgery) were seen in 58% of patients [323]. Late morbidity was usually linked to the type of urinary diversion (see also above) [326, 363]. 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 [364]. 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 [361, 365-369].

Table 7.6: Management of neobladder morbidity (30-64%) [370]**.**

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	ATB, no ureteral catheter removal Check the 3 drainages (ureters and neobladdder)
		Ureteral catheter (UC) obstruction	5cc saline UC injection to avoid the obstruction Increase volume infusion to increase dieresis
		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.	Anaemia badly tolerated or if myocardial cardiopathy history	Transfusion
		Pulmonary embolism	Heparinotherapy
		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	UC accidentally dislodged	Indwelling leader to raise the UC
		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 ASAP
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)

Grade IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.	Rectal necrosis	Colostomy
		Neobladder rupture	Nephrostomy and indwelling catheter/surgery for repairing neobladder
		Severe sepsis	ATB and check all the urinary drainages and CT 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.		

ASAP = as soon as possible; ATB = antibiotics; CNS = central nervous system; CT = computed tomography; IC = intensive care; ICU = intensive care unit; UC = urethral catheter.

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% [371]. Recent external validation of post-operative nomograms for bladder-cancer-specific mortality showed similar results, with bladder-cancer-specific survival of 62% [372].

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 [167]. However, the five-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34-43% [166, 167, 373]. In a surgery-only study, the 5-year recurrence-free survival was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [167].

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 [374].

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

Summary of evidence	LE
For MIBC, 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 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 > three 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, and the final decision should be based on a balanced discussion between patient and 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*
Lymph node dissection must be an integral part of cystectomy.	A
Preserve the urethra if margins are negative.	
Check the urethra regularly if no bladder substitution is attached.	B

*Upgraded following EAU Working Panel consensus.
LND = lymph node dissection; MIBC = muscle-invasive bladder cancer.

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

Diagnosis
- Cystoscopy and tumour resection
- Evaluation of urethra[1]
- CT imaging of abdomen, chest, UUT
- MRI can be used for local staging

[1] - Males: biopsy apical prostatic urethra or frozen section during surgery

- Females: biopsy of proximal urethra or frozen section during surgery

Findings
- pT2-4a, clinical N0M0 urothelial carcinoma of the bladder

pT2N0M0 selected patients
- Multimodality bladder sparing therapy can be considered for T2 tumours (Note: alternative, not the standard option)

Neoadjuvant chemotherapy[2]
- Should be considered in selected patients
- 5-7% 5 year survival benefit

[2] - Neoadjuvant radiotherapy is not recommended

Radical cystectomy
- Know general aspects of surgery
  o Preparation
  o Surgical technique
  o Integrated node dissection
  o Urinary diversion
  o Timing of surgery
- A higher case load improves outcome

Direct adjuvant chemotherapy
- Not indicated after cystectomy

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 [375-377].

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 [378]. 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 [379].

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
In patients with symptoms, palliative cystectomy may be offered.	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 first be screened 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 [380]. 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 [380]. 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% [381]. 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% [380]. 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)*
TURB 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 [382]. 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 [383]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [384, 385]. A prospective study by Solsona *et al.*, which included 133 patients with a radical TURB and re-staging negative biopsies, has recently reported a 15-year follow-up [385]. 30% 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 [386].

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 for BC is 60-66 Gy, with a subsequent boost using external RT or interstitial BT. 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 [387]. Acute diarrhoea is even more reduced with intensity-modulated RT [388]. 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 [389].

In 2007 long-term results were reported by Chung *et al.* [390]. 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 [391], although this was not the case in a recent retrospective review using a propensity score analysis [392].
> 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 (CRs). In general, a clinical CR rate of up to 56%, as reported in some series, must be weighed against a staging error of > 60% [393, 394]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival [190], 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 [188, 217, 395, 396]. Neoadjuvant chemotherapy with 2-3 cycles of methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) or cisplatin, methotrexate plus vinblastine (CMV) has led to a downstaging of the primary tumour in different prospective series [188, 217, 395]. 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 [188, 217, 395, 397-404].
> 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 [221].
> 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 [190]. However, this approach cannot be recommended for routine use.

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 [405].

There are no completed RCTs to compare the outcome of MMT with the gold standard, RC, but this approach has been shown superior to RT alone [406, 407]. 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 [406]). 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 [408]. 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 [408] whilst single-phase treatment is more commonly used elsewhere [406]. For radiosensitising chemotherapy, cisplatin [409] or mitomycin C plus 5-fluorouracil can be used [406], but also other schedules have been used. In particular, hypoxic cell sensitisation with nicotinamide and carbogen has been evaluated in a large phase 3 trial [410]. In a recent phase 1 trial Gemcitabine was used [411]. The regimen was well tolerated with promising results.

With MMT 5-year CSS and OS rates are achieved from 50-82% and from 36-74% respectively [387, 406, 409, 410, 412-414]. Salvage cystectomy rates are 10–30% [406, 409, 414]. There are data that major complication rates are similar for salvage and primary cystectomy [415]. The majority of recurrences post-MMT are non invasive and can be managed conservatively [406]. 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 [416]. 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.

7.6.4.1 Summary of evidence and recommendations for multimodality treatment in MIBC

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 lymph node positive (N+) disease without clinically detectable metastases (M0) is under debate [415, 417] and is still infrequently used [418].

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 intolerability of chemotherapy, due to post-operative morbidity [419].

There is limited evidence from adequately conducted and accrued randomised phase III trials in favour of the routine use of adjuvant chemotherapy [417, 420-425]. Individual patient data from six randomised trials [414, 426-429] of adjuvant chemotherapy were included in one meta-analysis [204] 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 [417]. In these trials, three or four cycles of cisplatin, methotrexate and vinblastine (CMV), cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [430], and one trial used cisplatin monotherapy [428]. These data were not convincing enough to give an unequivocal recommendation for the use of adjuvant chemotherapy.

In a more recent meta-analysis [421], an additional three studies were included [422-424]. 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 [421]. For one trial, only an abstract was available at the time of the meta-analysis [423], 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) [422, 423]. The hazard ratio (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 disease-free survival (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 lymph node dissection showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) [HR: 0.75; CI: 0.62-0.90] [431]. 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 [432].

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 lymph node metastases only, and with a good performance status [401, 433, 434]. With the most recent meta-analysis, the positive role of adjuvant chemotherapy for BC has been strengthened, however, still with a poor level of evidence [421]. 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.	C

7.8   Metastatic disease

7.8.1   Introduction

Half of the patients with muscle-invasive urothelial cancer (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 [435]. Before the development of effective chemotherapy, patients with metastatic urothelial cancer rarely had a median survival that exceeded 3-6 months [436].

7.8.1.1   Prognostic factors and treatment decisions

Prognostic factors are crucial for assessing phase II study results and stratifying phase III trials [399, 403]. In a multivariate analysis, Karnofsky performance status (PS) of ≤ 80% and presence of visceral metastases were independent prognostic factors of poor survival after treatment with MVAC [403]. They have also been validated for newer combination chemotherapy regimens [437-439].

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 [440]. Cisplatin, using different schedules, has also been administered in patients with a glomular filtration rate (GFR) down to 40 mL/min. The respective studies were mostly small sized phase I and II trials [441-444]. One phase III trial used a cut off for cisplatin eligibility of ≥ 50 mL/min [445].

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. There are several definitions by which patients can be selected as potentially fit or unfit for chemotherapy, but age is not among them [446].

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 [447]. The EORTC definitions were GFR < 60 mL/min and/or PS 2.

An international survey among BC experts [448] 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 and peripheral neuropathy; and New York Heart Association (NYHA) class III heart failure [449].

More than 50% of patients with urothelial cancer are not eligible for cisplatin-based chemotherapy [450-453]. 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 [450, 454].

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 [455, 456]. 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 6-9 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 [457]). Methotrexate, vinblastine, adriamycin plus cisplatin 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 [433]. The major difference between the above-mentioned combinations is toxicity. The

lower toxicity of GC [153] has resulted in it becoming a new standard regimen [458]. Methotrexate, vinblastine, adriamycin plus cisplatin is better tolerated when combined with granulocyte colony-stimulating factor (G-CSF) [458, 459].

High-dose intensity MVAC (HD-MVAC) 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 [460, 461]. 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 lymph nodes vs. 29% and 33% at extranodal sites [460]. 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 [433].

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 [462]. 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. G4 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 grade 4 thrombocytopenia and thrombocytopenia-induced bleeding (11.4% vs. 6.8%). PCG is one 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 [463].

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 [464-471].

7.8.6   *Chemotherapy in patients unfit for cisplatin*
Up to 50% of patients are ineligible for cisplatin-containing chemotherapy [449]. 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 [447]. The ORR and SAT were both 26% for the former group, and 20% and 24%, respectively, for the latter group [447]. Recent phase III data have confirmed these results [439].

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) [440]. 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 [472] oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [456]. 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 [455].

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 secondline combination [436, 470, 473].

Vinflunine, a novel third-generation vinca alkaloid, provided promising results in phase II trials [474]. 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 [475]. 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 urothelial cancer, this trial reached the highest level of evidence ever reported. Currently, vinflunine is the only approved second-line treatment.

7.8.8 Low-volume disease and post-chemotherapy surgery

With cisplatin-containing combination chemotherapy, excellent response rates may be obtained in patients with lymph node 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 [433, 461, 476, 477]. 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 [478-492]. 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 [404, 493, 494].

7.8.9 Treatment of bone metastases

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic urothelial cancer is 30-40% [495]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [496]. 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 [497]. Denosumab is a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor-KB 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 urothelial carcinoma [498]. 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 [496].

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 [499]. For denosumab, no dose adjustments are required for variations in renal function.

7.8.10 Summary of evidence and recommendations for metastatic disease

Summary of evidence	LE
In a first-line setting, 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 ≥ 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.	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.	3
Zoledronic acid and denosumab have been approved for all cancer types including urothelial cancer, because they reduce and delay skeletal related events in metastatic bone disease.	1b

Recommendations	GR
First-line treatment for fit patients:	
Use cisplatin-containing combination chemotherapy with GC, PCG, MVAC, preferably with G-CSF, or HD-MVAC with G-CSF.	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 PS2 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 by a problem of 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; PS = performance status; PCG = paclitaxel, cisplatin, gemcitabine.

7.8.11 **Biomarkers**

Modest disease control rates, with sporadic marked responses, in some patients with urothelial BC 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 [500], serum vascular endothelial growth factor [501], urinary and tissue basic fibroblast growth factor [502], urinary (wild-type and mutant) and tissue fibroblast growth factor receptor-3 [503], and more recently, thrombospondin-1 [504], circulating tumour cells [505, 506], and multidrug resistance gene expression [507]. Although a few biomarkers have shown potential, as yet, there is insufficient evidence to support its routine clinical use (LE: 3).

7.8.11.1 Recommendation on 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: Algorithm for the management of metastatic urothelial cancer

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                        ┌─────────────────────────────┐
                        │   Patient characteristics   │
                        │      PS 0-1/ 2/ >2          │
                        │    GFR ≥/< 60 mL/min        │
                        │        Comorbidities        │
                        └─────────────────────────────┘
```

	CISPLATIN?	
YES	NO	NO

| PS 0-1 and GFR ≥ 60 mL/min

 STANDARD[403,439] GC
 MVAC
 HD MVAC
 PCG | PS 2 or GFR < 60 mL/min

 Comb. chemo: Carbo-based | PS ≥ 2 and GFR < 60 mL/min

 NO comb chemo[399] Studies, monotherapy, BSC |

Second-line treatment

| PS 0-1 | PS ≥ 2 |

| Progressions
1. > 6-12 mo after first-line chemo, adequate renal function[433,459,462]
 a. re-exposition to first-line treatment (cisplatin-based)
 b. clinical study | 2. Progression > 6-12 mo after first-line chemo therapy, PS 0-1, impaired renal function[433]
 a. vinflunine
 b. clinical study | 3. Progression < 6-12 mo after first-line chemotherapy, PS 0-1[433]
 a. vinflunine
 b. clinical study | a. Best supportive care
b. clinical study |

BSC = best supportive care; GC = gemcitabine plus cisplatin; GFR = glomular 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
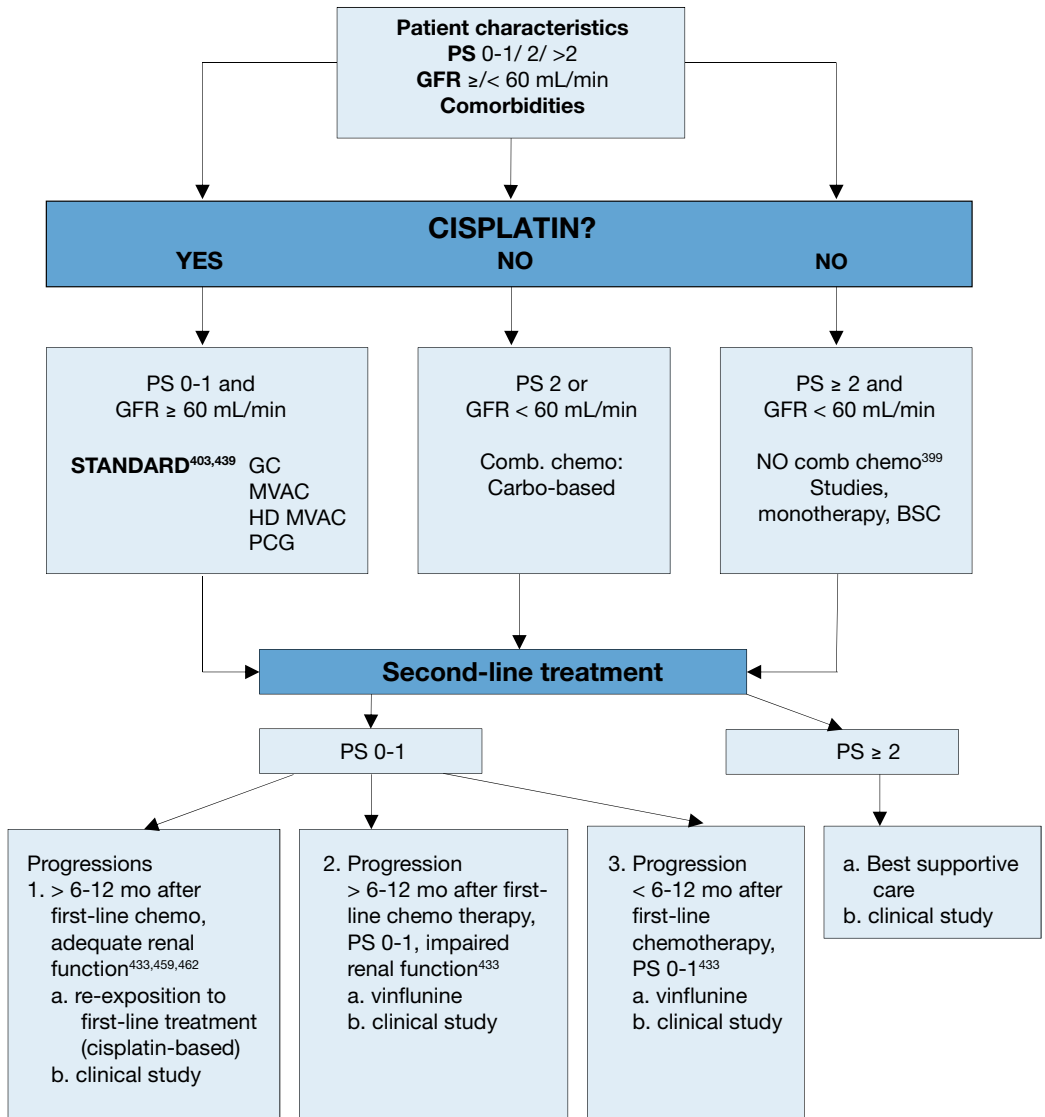
7.9.1 Introduction

The evaluation of health-related quality of life (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 [508], EORTC QLQ-C30 [509], EORTC QLQ-BLM (muscle-invasive bladder cancer module) [510], and SF (Short Form)-36 [511, 512] and recently the BCI questionnaire specifically designed and validated for BC patients [513].

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 in life [514].

7.9.2 Choice of urinary diversion

There is controversy about which type of urinary diversion is best for a patient's HRQoL [233]. Some studies have not demonstrated any difference in HRQoL [515, 516]. Nevertheless, most patients stated that, given a choice, they would still opt for an orthotopic diversion rather than an ileal conduit [517]. Another study reported that, although urinary function is better in conduit patients, the urinary bother is the same in both diversion groups, resulting in the same HRQoL evaluation [518].

Due to improved surgical techniques in orthotopic bladder substitution, some recent studies are supportive of continent bladder substitutes [360, 510, 519]. 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 [520]. 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 [518, 519]. 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 CIC to a certain amount what 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 [521].

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 [522]. There is limited literature describing HRQoL in BC patients receiving palliative care [523], but there are reports of bladder-related symptoms relieved by palliative surgery [379], RT [524], and/or chemotherapy [525].

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 [130, 387, 525-529].

7.9.4   Summary of evidence and recommendations for HRQoL

Summary of evidence	LE
No randomised, prospective 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 higher HRQoL has not been sufficiently substantiated.	
Important determinants of (subjective) QoL 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

HRQoL = health-related quality of life; MIBC = muscle-invasive bladder cancer.

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 [530].

Nomograms on CSS following RC have been developed and externally validated. However, their wider use cannot be recommended until further data becomes available [531, 532].

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 [533, 534]. 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 [535].

8.2   Site of recurrence
8.2.1   Local recurrence
Local recurrence takes place in soft tissues at the original surgical site or lymph nodes in the area of LND. Lymph node involvement above the aortic bifurcation can be considered metastatic recurrence [533].

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 lymph node status are predictive for pelvic recurrence, as well as positive margins, extent of LND, and peri-operative chemotherapy [536].

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 is with systemic chemotherapy, local surgery, or RT [535].

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 [537]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with lymph node involvement (range 52–70%) [538].
        The most likely sites for distant recurrence are lymph nodes, 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 [539-541].
        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 [533, 534]. 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 [487, 494].

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 [535].

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%) [542-545] is significantly less than after non-orthotopic diversion (6.4–11.1%) [536, 542, 544].

There is limited data and agreement about urethral follow-up, with some recommending routine surveillance with urethral wash and urine cytology [545], and others doubting the need for routine urethral surveillance [543, 546, 547]. Urethral washes and urine cytology do not appear to affect survival [546, 548]. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptomatically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [535].

Treatment is influenced by local stage and grade of urethral occurrence:
• in urethral CIS, BCG instillations have success rates of 83% [545];
• in invasive disease, urethrectomy should be performed if the urethra is the only site of disease;
• in distant disease, systemic chemotherapy is indicated [549].

Upper urinary urothelial carcinomas (UTUC) 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 [535].

A recent 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 [550]. 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 threefold, while positive ureteral or urethral margins increase the risk by sevenfold. Radical nephroureterectomy can prolong survival [551].

8.2.3   Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	LE	Recommendations	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 (NMIBC/ CIS or positive ureteral margins.		See EAU guidelines on Upper Urinary Tract Carcinomas [1].	
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 lymph node involvement. The suggested follow-up includes four-monthly CT scans during the first year, six-monthly until the 3rd 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 (> three years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used to assess the UUT [550].

8.3   Follow-up of functional outcomes and complications
Apart from oncological surveillance, patients submitted for urinary diversion deserve functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first five years follow-up.

This rate increases over time, and exceeds 54% after fifteen years follow-up. Therefore, long-term follow-up of functional outcomes is desirable [535] (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 [535]. Especially in women approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [521]. Recently also a 21% increased risk of fractures was described as compared to no cystectomy, due to chronic metabolic acidosis and subsequent long-term bone loss [552].

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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: http://www.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
Primary Urethral Carcinoma

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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 [2] of the full text versions).

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.

1.2   Panel composition

The EAU Guidelines Panel on Muscle-invasive and Metastatic Bladder Cancer (MIBC) is responsible for this publication. This is an international multidisciplinary group of clinicians, including 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 harbouring 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 first update of this document.

1.3.1   *Summary of changes*

The literature for the complete document has been assessed and updated, where relevant.
Key changes for the 2015 publication:
* Evaluation of recent data on prognostic factors on oncologic outcomes in primary UC;
* Evaluation of recent data on the degree of concordance between clinical and pathologic staging;
* Evaluation of recent data on distal urethrectomy in men;
* Evaluation of recent data on the prognostic effect of multimodal treatment in advanced primary UC.

Conclusions and recommendations have been rephrased and added to throughout the document, with no changes in the level of evidence (LE) and grade of recommendation (GR). These changes can be found in the following sections:

6.2   Predictors of survival in primary urethral carcinoma

Summary of evidence	LE
Risk factors for survival in primary UC 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

7.1   Treatment of localised primary urethral carcinoma in males

Recommendation	LE	GR
Offer distal urethrectomy as an alternative to penile amputation in localised anterior urethral tumours, if surgical margins are negative.	3	B

7.2.2   *Radiotherapy*

Recommendation	LE	GR
Offer local radiotherapy as an alternative to urethral surgery to women with localised urethral tumours, but discuss local toxicity.	3	C

7.3.2 ***Preoperative chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra***

Summary of evidence	LE
In locally advanced UC, 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
Use cisplatinum-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

SCC = squamous cell carcinoma; UC = urethral carcinoma.

2. METHODS

2.1 Data identification
An updated systematic literature search was performed to identify studies reporting data on urethral malignancies since the last search on October 15th 2012 until August 15th 2014. Medline was searched using the controlled vocabulary of the Medical Subject Headings (MeSH) database, along with a free-text protocol, using one or several combinations of the following terms: *adenocarcinoma, adjuvant treatment, anterior, chemotherapy, distal urethral carcinoma, lower, neoadjuvant, partial, penectomy, penile-preserving surgery, posterior, primary, proximal urethral carcinoma, radiotherapy, recurrence, risk factors, squamous cell carcinoma, survival, transitional cell carcinoma, urethra, urethrectomy, urethral cancer, urinary tract, and urothelial carcinoma*. No randomised controlled trials were identified and articles were selected based on study design, treatment modality and long-term outcomes. Older studies (> 10 years) were considered if they contained historically relevant data or in the absence of newer data.

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 aim 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 urethral carcinoma and its predictive value on clinical decision-making;
- The (long-term) efficacy of urethral-sparing surgery and radiochemotherapy for genital preservation in localized tumours;
- The prognostic impact of neoadjuvant and adjuvant treatment modalities in locally advanced disease;
- The prognostic significance of salvage treatment in locally recurrent primary urethral carcinoma.

These reviews will be performed using standard Cochrane systematic review methodology;
http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

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 EU 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 urethral carcinoma. Clear cell adenocarcinoma 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 SCC (16-22%) and adenocarcinoma (AC) (10-16%) [7, 8]. A recent SEER analysis of 2,065 men with primary urethral cancer (mean age: 73 years) found that urothelial carcinoma 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 urothelial carcinoma 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 Tumor, Node, Metastasis (TNM) staging system

In men and women, UC is classified according to the 7th 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 urethral diverticulum, stage T2 is not applicable as urethral diverticula are lacking periurethral muscle [26].

Table 4.1: TNM classification (7th edition) for UC [6].
Primary tumour stage is separated into UC and UC of the prostate

T - Primary Tumour (men and women)	
Tx	Primary tumour cannot be assessed
Tis	Carcinoma *in situ*
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following structures: corpus spongiosum, prostate, peri-urethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck
T4	Tumour invades other adjacent organs
Primary tumour in prostatic urethra	
Tx	Primary tumour cannot be assessed
Tis pu	Carcinoma *in situ* in the prostatic urethra
Tis pd	Carcinoma *in situ* in the prostatic ducts
T0	No evidence of primary tumour
T1	Tumour invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement)
T2	Tumour invades any of the following structures: corpus spongiosum, prostatic stroma, periurethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, beyond prostatic capsule, bladder neck
T4	Tumour invades other adjacent organs
N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph-node metastasis
N1	Metastasis in a single lymph node $\leq$ 2 cm in greatest dimension
N2	Metastasis in a single lymph node > 2 cm in greatest dimension or in multiple nodes
M - Distant Metastasis	
Mx	Distant metastasis cannot be assessed
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].

Table 4.2: Histopathological grading of urothelial and non-urothelial primary UC [27]

Urothelial carcinoma	
PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated

Non-urothelial UC	
Gx	Tumour grade not assessable
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

Recommendation	LE	GR
Use the 2009 TNM classification and WHO 2004 grading system for pathological staging and grading of primary urethral carcinoma.	3	B

TNM = Tumour, Node, Metastasis; WHO = World Health Organization.

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) [26-28]. 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 [28].

5.2 Clinical examination
In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [29]. 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, describing location, size and mobility [30].

5.3 Urinary cytology
The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55% and 59% [31]. 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.

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 [29]. 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, 32]. 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 (at 5 and 7 o'clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [33].

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 [34]. Imaging for regional lymph node metastases should concentrate on inguinal and pelvic lymph nodes, using either MRI or CT. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (≥ cT1N0M0) [34-38]. If imaging of the remainder of the urothelium is required, then CT should include CT urography with an excretory phase [39].

5.6 Regional lymph nodes

Enlarged lymph nodes in UC often represent metastatic disease [40, 41]. In men, lymphatics from the anterior urethra drain into the superficial- and deep inguinal lymph nodes and subsequently to the pelvic (external, obturator and internal iliac) lymph nodes. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic lymph nodes. In women, the lymph of the proximal third drains into the pelvic lymph node chains, whereas the distal two-thirds initially drain into the superficial- and deep inguinal nodes [42, 43].

Nodal control in UC can be achieved either by regional lymph node dissection [29], radiotherapy [44] or chemotherapy [40]. Currently, there is still no clear evidence to support prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with UC. However, in patients with clinically enlarged inguinal/pelvic lymph nodes or invasive tumours, regional lymphadenectomy should be considered for initial treatment because cure might still be achievable with limited disease [29].

Summary of evidence	LE
Patients with clinically enlarged inguinal or pelvic lymph nodes often exhibit pathological lymph node metastasis.	3

Recommendations	LE	GR
Use urethrocystoscopy with biopsy and urinary cytology to diagnose urethral carcinoma.	3	B
Assess the presence of distant metastases by CT of the thorax and abdomen	3	B
Use pelvic MRI to assess the local extent of urethral tumour (mapping tumour extension).	3	B

CT = computed tomography; MRI = magnetic resonance imaging.

6. PROGNOSIS

6.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the mean 1- and 5-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 5- and 10-year OS rates of 46% and 29%, respectively. Cancer-specific survival (CSS) at 5 and 10 years was 68% and 60%, respectively [8].

6.2 Predictors of survival in primary urethral carcinoma

In Europe, mean 5-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, 45];
* stage, grade, nodal involvement [41] and metastasis [24];
* tumour size and proximal tumour location [24];
* extent of surgical treatment and treatment modality [24, 45];
* underlying histology [7, 25, 45];
* presence of concomitant bladder cancer [32].

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 [45].

Summary of evidence	LE
Risk factors for survival in primary UC 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 [29]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [46]. 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 lymph node disease [47]. This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have also been reported in a recent series [48].

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 via an appendico-vesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women [29].

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 [49-51]. In long-term series with a median follow-up of 153-175 months, local recurrence rates in women undergoing partial urethrectomy with intraoperative 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 [50].

Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal UC, have also resulted in a considerable local failure rate 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 [49].

7.2.2 Radiotherapy

In women, radiotherapy was investigated in several older long-term series with a medium follow-up of 91-105 months [44, 47]. With a median cumulative dose of 65 Gy (range: 40-106 Gy), the 5-year local control rate was 64% and 7-year CSS was 49% [44]. Most local failures (95%) occurred within the first two years after primary treatment [47]. 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 [44]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [52]. 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 [44].

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 intraoperatively.	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 lymph-node-positive disease. Moreover, they have emphasised the critical role of surgery after chemotherapy for achieving 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 [53]. 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 significantly improved OS compared with those who were managed with chemotherapy alone [40].

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 [53-58]. 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 5-year overall- and disease-specific 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 [54].

Summary of evidence	LE
In locally advanced UC, cisplatin-based chemotherapy with curative intent prior to surgery improves survival compared to chemotherapy alone or surgery followed by chemotherapy.	4
In locally advanced 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 cisplatinum-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

SCC = squamous cell carcinoma

7.4 Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent Bacille-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC [59, 60]. Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs. 66%) [61]. Risk of understaging local extension of prostatic urethral cancer at TUR is increased, especially in patients with ductal or stromal involvement [62]. In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57 and 75% [59, 63]. 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 [64, 65]. In 24 patients with prostatic stromal invasion treated with radical

cystoprostatectomy, a lymph node mapping study found that 12 patients had positive lymph nodes, with an increased proportion located above the iliac bifurcation [66].

Summary of evidence	LE
Patients undergoing transurethral resection of the prostate for prostatic urothelial carcinoma prior to BCG treatment show superior complete response rates compared to those who do not.	3

Recommendations	LE	GR
Offer a urethra-sparing approach with TUR and BCG to patients with non-invasive urethral carcinoma or carcinoma *in situ* of the prostatic urethra and prostatic ducts.	3	C
In patients with non-invasive UC or carcinoma *in situ*, 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

BCG = Bacille-Calmette-Guérin; TUR = transurethral resection

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, urethrocytoscopy and cross-sectional imaging despite the lack of specific data.

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10.   CONFLICT OF INTEREST

EAU – ESTRO – SIOG Guidelines on
Prostate Cancer

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European
Association
of Urology

ESTRO
European SocieTy for
RADIOTHERAPY
& ONCOLOGY

SIOG
INTERNATIONAL SOCIETY
OF GERIATRIC ONCOLOGY

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) 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.

1.2 Panel composition

The PCa Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, a radiologist, a pathologist and a patient representative.

Section 6.3: Treatment - Definitive Radiotherapy, has been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO in the EAU PCa Guidelines Panel are (in alphabetical order): Prof.Dr. M. Bolla, Dr. A. Henry, Prof.Dr. M. 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/prostate-cancer/?type=panel.

1.2.1 *Acknowledgement*

The EAU PCa Guidelines Panel are most grateful for the support and considerable expertise provided by Prof.Dr. J-P. Droz, Emeritus Professor of Medical Oncology (Lyon, France) on the topic of 'Management of PCa in senior adults'. As a leading expert in this field, and prominent member of the International Society of Geriatric Oncology, his contribution has been invaluable.

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 2016 document presents a full update of the 2015 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 2016 EAU PCa Guidelines.

Key changes for the 2016 print:
- Chapter 4 - Classification and staging systems, the new 2014 International Society of Urological Pathology (ISUP) Consensus Conference findings have been included.
- Section 5.2.4 Diagnosis - The role of imaging; the key findings of the systematic review on the performance of prostate pre-biopsy multi parametric MRI in predicting prostate biopsy results, have been included [3]. The recommendations have been adapted accordingly.
- Section 6.2 - Radical prostatectomy, a new Section 6.2.6 - Indication and extent of pelvic lymph node dissection has been included.
- Section 6.4 - Options other than surgery and radiotherapy for the primary treatment of localised PCa, has been revised and restructured.
- Section 6.6 - Treatment: Metastatic PCa, has been completely revised.
- Section 6.10 - Treatment of PSA-only recurrence after treatment with curative intent,
  - Section 6.10.5.2 - Hormonal therapy; the key findings of a systematic review on 'The role of hormonal treatment in PCa patients with non-metastatic disease recurrence after local curative treatment' [4] have been included.
- Section 6.10.11 - Salvage lymph node dissection has been included as a new topic.
- Section 6.11 -Treatment: Castration-resistant PCa (CRPC), has been completely revised.

Changed recommendations and evidence summaries can be found in sections:

5.1.1 Guidelines for screening and early detection

Recommendation	LE	GR
Do not subject men to PSA testing without counselling on the potential risks and benefits.	3	B

PSA = prostate-specific antigen.

5.3.5 Guidelines for staging of PCa

Intermediate-risk PCa	LE	GR
In predominantly Gleason pattern 4, metastatic screening, include at least a cross-sectional abdominopelvic imaging, and a CT/MRI and bone-scan for staging purposes.	2a	A*
In predominantly Gleason pattern 4, use prostate mpMRI for local staging and metastatic screening.	2b	A

High-risk localised PCa/ High-risk locally advanced PCa	LE	GR
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	A

mpMRI = multiparametric magnetic resonance imaging; CT = computed tomography.

6.4.5 Summary of evidence and guidelines for experimental therapeutic options to treat clinically localised PCa

Summary of evidence	LE
The available short-term data does not prove equivalence.	2b
There is no reliable long-term comparative data to indicate that CSAP or HIFU leads to equivalent oncological outcomes compared with radical prostatectomy or EBRT.	3
PSA nadir values after ablative therapies may have prognostic value.	3
Focal therapy of any sort appears promising but remains investigational, with uncertainties surrounding follow-up and re-treatment criteria.	3

Recommendation	LE	GR
Only offer cryotherapy and HIFU within a clinical trial setting.	3	B

HIFU = high-intensity focused ultrasound.

6.6.7 Guidelines for hormonal treatment of metastatic prostate cancer

Recommendation	LE	GR
In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.	1a	A

6.10.4.6 Guidelines for imaging in patients with biochemical failure

PSA recurrence after RT	LE	GR
Choline PET/CT imaging is recommended to rule out lymph nodes or distant metastases in patients fit enough for curative salvage treatment	2b	B

PET/CT = positon emission tomography/computed tomography.

6.10.11.1 Guidelines for salvage lymph node dissection

Recommendation		GR
Discuss salvage 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.		

LND = lymph node dissection.

Summary of evidence	LE
No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy or chemotherapy) as no clear predictive factors exist.	3

2. METHODS

2.1 Data identification

For the 2016 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. systematic reviews with meta-analysis, randomised controlled trials, and prospective comparative studies) published in the English language. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between January 1st 2014 to April 24th 2015. A total of 1,792 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/prostate-cancer/?type=appendices-publications.

Specific sections of the text have been updated based on a systematic review 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:

- Section 5.2.4.2 - Multiparametric MRI (mpMRI)
  What is the performance of prostate pre-biopsy multi parametric MRI in predicting prostate biopsy results? [3].

- Section 6.10.5.2 - Hormonal therapy
  The role of hormonal treatment in PCa patients with non-metastatic disease recurrence after local curative treatment: A systematic review [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 (2). 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. In addition, the International Society of Geriatric Oncology (SIOG) and the European Society for Radiotherapy & Oncology (ESTRO) have endorsed the PCa Guidelines.

2.2 Review

The following sections were subjected to peer review prior to publication:
- 6.6. Treatment - Metastatic prostate cancer;
- 6.11. Treatment - Castration-resistant prostate cancer (CRPC).

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2017 update of the PCa Guidelines.

Ongoing systematic reviews include:
- What is the performance of prostate pre-biopsy multi parametric MRI in predicting prostate biopsy results? [3].
- Antibiotic prophylaxis for prostate biopsies: Risk factors for infection - what is the optimal antibiotic prophylaxis?
- What are the benefits and harms of extended, limited or no lymph node dissection during radical prostatectomy for prostate cancer? [5];
- How does biochemical recurrence following curative treatment for prostate cancer impact on overall survival, cancer-specific survival and development of metastatic disease? [6].

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Prostate cancer is the most common non-skin cancer in elderly males (> 70 years of age) in Europe. It is a major health concern, especially in developed countries with a greater proportion of elderly men in the general population. The incidence is highest in Northern and Western Europe (> 200 per 100,000 men), while rates in Eastern and Southern Europe have showed a continuous increase [7]. There is a survival difference between men diagnosed in Eastern Europe and those in the rest of Europe [8]. Overall, during the last decade, the 5-year relative survival percentages for PCa steadily increased from 73.4% in 1999-2001 to 83.4% in 2005-2007 [8].

With the expected increase in the life expectancy of men and the subsequent rise in the incidence of PCa, the disease's economic burden in Europe is also expected to increase. It is estimated that the total economic costs of PCa in Europe exceed € 8.43 billion [9], with a high proportion of the costs occurring in the first year after diagnosis. In European countries with available data (UK, Germany, France, Italy, Spain, the Netherlands), this amounted to € 106.7-179.0 million for all PCa patients diagnosed in 2006.

3.2 Risk factors and chemoprevention

Epidemiological studies have shown strong evidence for a genetic predisposition to PCa, based on two of the most important factors, racial/ethnic background and family history [10, 11]. Genome-wide association studies have identified 100 common suseptibility loci who contribute to the risk for PCa [12].

A small subpopulation of men with PCa (about 9%) have true hereditary PCa. This is defined as three or more affected relatives, or at least two relatives who have developed early-onset disease, i.e. before the age of 55 [11]. More than 70 PCa susceptibility loci, explaining ~30% of the familial risk for this disease, have been identified [13]. Patients with hereditary PCa usually have a disease onset six to seven years earlier than spontaneous cases, but do not differ in other ways [11].

The frequency of incidentally- and autopsy-detected cancers is roughly the same in different parts of the world [14]. This finding is in sharp contrast to the incidence of clinical PCa, which varies widely between different geographical areas, being high in the USA and Northern Europe and low in South-East Asia. If Japanese men move from Japan to Hawaii, their risk of PCa increases. If they move to California their risk increases even more, approaching that of American men [15].

These findings indicate that exogenous factors affect the risk of progression from so-called latent PCa to clinical PCa. Factors such as diet, sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation [16, 17] and occupational exposure have all been discussed as being aetiologically important [17]. Prostate cancer ought to be an ideal candidate for exogenous preventive measures, such as dietary and pharmacological prevention, due to the following specific features:
- high prevalence;
- long latency;
- endocrine dependency;
- availability of serum markers (prostate-specific antigen [PSA]);
- the histological precursor lesion prostatic intraepithelial neoplasia [16].

However, there is currently no strong evidence to suggest that dietary interventions can reduce the risk of PCa. Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) showed a weak correlation between insulin-like growth factor-I (IGF-1) levels and high intake of protein form dairy products and an increased risk of PCa [18]. The outcome of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) was negative, and therefore vitamin E and selenium are not recommended for the prevention of PCa [19]. Similarly, a meta-analysis of eight randomised controlled trials (RCTs) comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [20].

Metabolic syndrome is weakly and non-significantly associated with the risk of PCa, but associations vary with geography. Among single components of the syndrome (body mass index, dysglycaemia or dyslipidaemia, high triglycerides, low high-density lipoprotein (HDL) cholesterol) only hypertension and waist circumference > 10^2 cm were associated with a significantly greater risk of PCa, increasing the risk by 15% (p = 0.035) and 56% (p = 0.007), respectively [21]. Currently, there are no data to suggest that medical intervention would effectively reduce progression of PCa.

The role of medication in the development of PCa has been investigated in several subgroups. A recent study in hypogonadal men receiving testosterone therapy did not show an increased risk of PCa [22].

Furthermore there are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa [23, 24].

Several 5-alpha-reductase inhibitors (5-ARIs) have been studied to assess their effect on reducing the risk of developing PCa. Although it seems that 5-ARIs have a potential benefit in 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 increased risk of high-grade PCa [25-27]. None of the available 5-ARIs have been approved for this indication.

Several studies have been published on a putative correlation between statin use and PCa incidence: a recent meta-analysis and the results of the REDUCE study did not confirm a preventive effect of statins on PCa risk [21, 28].

In summary, hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on the risk of progression. There is, as yet, insufficient evidence to recommend lifestyle changes (such as a reduced intake of animal fat and an increased intake of fruit, cereals and vegetables) in order to decrease the risk. But such lifestyle modifications might be associated with other non-specific benefits and must therefore be encouraged.

3.2.1   Guideline for preventative measures
At this moment in time no definitive recommendation can be provided for preventive measures due to the lack of conclusive data.

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 to make recommendations on their treatment. Throughout this Guideline the 2009 Tumour, Node, Metastasis classification for staging of PCa (Table 4.1.1) [29] and the EAU risk group classification essentially based on D'Amico's classification system for PCa is used (Table 4.1.2) [30]. 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 [29]

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour not palpable or visible by imaging	
	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 confined within the prostate[1]	
	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[2]	
	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 nodes[3]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis[4]	
M - Distant metastasis[5]		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] *Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.*

[2] *Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.*

[3] *The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.*

[4] *Laterality does not affect the N-classification.*

[5] *When more than one site of metastasis is present, the most advanced category should be used.*

4.2 Gleason score and ISUP 2014 grade groups

The (2005 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 [31]. 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 [32, 33] has introduced the concept of the grade groups of PCa, 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 codify the clinically highly significant distinction between Gleason score 7 (3 + 4) and 7 (4 + 3) PCa.

The grade groups represent a compression of Gleason scores ≤ 6 in grade group 1 and Gleason scores 9-10 in grade group 5, whereas Gleason score 7 is expanded to grade group 2, i.e. 7 (3 + 4) and grade group 3, i.e. 7 (4 + 3). The ISUP 2014 prostate cancer grade groups therefore range from 1-5, see table 4.2.1.

Table 4.2.1 International Society of Urological Pathology 2014 grade groups

Gleason score	Grade group
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

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

PSA = prostate-specific antigen.

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 [34]. 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 [35]. However, there is still no level 1 evidence that PSA mass screening is cost-effective in reducing PCa mortality [36].

Currently, screening for PCa is one of the most controversial topics in the urological literature [37]. Three large prospective RCTs published data on screening in 2009 [38-40]. Heated discussions and debates resulted in many conflicting positions and policy papers. Some authors argue that the use of current American Urological Association (AUA) guidelines [41] or the U.S. Preventive Services Task Force recommendations for screening [42] may lead to a substantial number of men with aggressive disease being missed [43, 44]. Recently 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 [45]. 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 [36], which has been updated since [46] presents the main overview. 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 these 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. the biopsy) was not associated with any mortality in the selected papers, which is in contrast with other known data [26, 27].

The impact on the patient's overall QoL is still unclear [47-49], 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) [50]. The key message is that with extended follow up, the mortality reduction remains unchanged (21%, and 29% after noncompliance 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 [51].

Table 5.1.1 Follow-up data from the ERSPC study [50]

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 10-15 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 with a family history of PCa (both paternal and maternal [52]) and age > 45 years, or African-Americans [53]. In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [54, 55] are also at increased risk of PCa metastasis or death several decades later. The long-term survival and QoL benefits of such an approach remains to be proven at a population level. Recently, as for breast cancer, a genetic abnormality likely to be associated with an increased risk has been shown prospectively, especially for BRCA2 [56]. Several new biological markers such as TMPRSS2-Erg fusion, PCA3, kallikreines [57, 58] or several genetic markers [59-62] have been shown to add sensitivity and specificity on top of PSA, lowering over-diagnosis. At this time there is too limited data to base a recommendation on. Also a population-based survival benefit has not yet been demonstrated.

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-risk-calculators;
- 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 [63].

Informed men requesting an early diagnosis should be given a PSA test and undergo a digital rectal examination (DRE) [64]. 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 2 years for those initially at risk, or postponed up to 8-10 years in those not at risk [65].

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 15-year life expectancy are unlikely to benefit based on data from the 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 [66].

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 7.1, Deferred treatment). It is important to realise that breaking the link between diagnosis and active treatment is the only

way to decrease overtreatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.

From a public health point of view, mass screening of PCa is not indicated. However, early diagnosis on an individual basis is possible based on DRE and PSA testing. Individual patient screening requires informed consent from the patient following a full discussion with their physician on the pros and cons of the complete procedure, taking into account the patient's risk factors, age and life expectancy. The interval for follow-up screening depends on age and baseline PSA level.

5.1.1 *Guidelines for screening and early detection*

Recommendation	LE	GR
Do not subject men to 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 10-15 years.	3	B
Offer early PSA testing in men at elevated risk of having PCa: • 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 2 years for those initially at risk: • 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 8 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 based on data from the PIVOT and the ERSPC trials.	3	A

ERSPC = European Randomized Study of Screening; PCa = prostate cancer; PIVOT = Prostate Cancer Intervention Versus Observation Trial; PSA = prostate-specific antigen.

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 [67]. Suspect DRE in patients with PSA level ≤ 2 ng/mL has a positive predictive value of 5-30% [68]. Abnormal DRE is associated with an increased risk of higher Gleason score and is an indication for biopsy [69, 70].

5.2.2 *Prostate-specific antigen*

The use of PSA as a serum marker has revolutionised PCa diagnosis [71]. 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) [72].

There are no agreed standards defined for measuring PSA [73]. PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [74]. Table 5.2.1 demonstrates the occurrence of Gleason ≥ 7 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 [75].

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) [76];
• PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [77].

Prostate specific antigen velocity and PSA-DT may have a prognostic role in treated PCa [78], 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 [79-82].

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 [83]. 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) [84].

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 [85, 86].

5.2.2.5   PCA3 marker
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 [87-90].
          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 unconfirmed [91]. 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 [92].

5.2.2.6   Guidelines for risk-assessment of asymptomatic men

Recommendation	LE	GR
Offer further risk-assessment to asymptomatic men with a PSA between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: • risk-calculator; • an additional serum or urine-based test (e.g. PHI, 4Kscore or PCA3) or imaging.	3	C

PSA = prostate specific antigen; PHI = Prostate Health Index test.

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 [93]. Risk stratification is a potential tool for reducing unnecessary biopsies [93].

Limited PSA elevation alone should not prompt immediate biopsy. PSA level should be verified after a few weeks using the same assay under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory [94, 95]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [96].

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 [97, 98].

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 for risk estimates);
- suspicious DRE, 5-30% cancer risk [67, 68];
- atypical small acinar proliferation (i.e., atypical glands suspicious for cancer), 40% risk [99];
- extensive (multiple biopsy sites, i.e., ≥ 3) high grade prostatic intraepithelial neoplasia (HGPIN), ~30% risk [99, 100];
- a few atypical glands immediately adjacent to high grade prostatic intraepithelial neoplasia (i.e., PINATYP), ~50% risk [101];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade prostate carcinoma [102];
- positive multiparametric MRI findings (see Section 5.2.4).

Additional information may be gained by the Progensa DRE urine test for PCA3, the serum 4K and PHI test 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 [92]. 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 recent 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 [103]. Given the limited currently available data, no recommendation can be made regarding its routine application.

Table 5.2.3.2 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 [104].

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 [105]. 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 [106].

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 12 core biopsies are recommended [107], with > 12 cores not being significantly more conclusive [108, 109].

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 [110].

5.2.3.6   Seminal vesicle biopsy
Indications for seminal vesicle (staging) biopsies are poorly defined. At PSA > 15 ng/mL, the odds of tumour involvement are 20-25% [111]. 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 multiparametric magnetic resonance imaging (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 [112].

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 [113]. Increased quinolone resistance [114] is associated with a rise in severe post-biopsy infection [115].

5.2.3.9   Local anaesthesia prior to biopsy
Ultrasound-guided periprostatic block is recommended [116]. It is not important whether the depot is apical or basal. Intrarectal instillation of local anaesthesia is inferior to periprostatic infiltration [117].

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 5.2.2 [118]. Severe post-procedural infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance [119].
Low-dose aspirin is no longer an absolute contraindication [120].

Table 5.2.2: 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   **Role of imaging**
5.2.4.1   TRUS and US-based techniques
Grey-scale TRUS is not reliable at detecting PCa [121]. Thus, there is no evidence that US-targeted biopsies can replace systematic biopsies. New sonographic modalities such as sonoelastography and contrast-enhanced US are being investigated. Currently there is not enough evidence for their routine use [122].

5.2.4.2   Multiparametric magnetic resonance imaging (mpMRI)
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 excellent sensitivity for the detection and localisation of Gleason score ≥ 7 cancers (see Table 5.2.3) [123-126].

Table 5.2.3: PCa detection rates (%) by mpMRI for tumour volume and Gleason score [126]

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%

Many single-centre studies suggest that mpMRI 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 [127]. The association of systematic biopsies and biopsies targeted on mpMRI abnormalities (MRI-Tbx) may also better predict the final pathological grade found at prostatectomy [128]. As a result, some authors proposed performing mpMRI before prostate biopsy, to increase the detection of aggressive cancers and reduce the over-detection of non-significant foci [129-132]. One recent meta-analysis confirmed that, in men with an abnormal mpMRI, MRI-Tbx had a higher detection rate of clinically significant PCa compared to TRUS biopsy (sensitivity 0.91, [95% CI: 0.87-0.94] vs. 0.76, [95% CI: 0.64- 0.84]) and a lower rate of detection of insignificant PCa (sensitivity 0.44, 95% CI: 0.26-0.64 vs. 0.83, 95% CI: 0.77-0.87). However, sub-group analysis showed that MRI-Tbx markedly improved the detection of significant PCa in the repeat biopsy setting (relative sensitivity 1.62 [95% CI: 1.02-2.57]) but not in men with an initial biopsy (relative sensitivity 0.97 [95% CI: 0.94-1.01]) [133]. Another systematic review reached similar conclusions [122]. Two recent RCTs not included in the meta-analyses and performed in patients undergoing an initial biopsy, yielded contradictory results as to whether or not the association of systematic biopsies and MRI-Tbx had a higher detection rate than systematic biopsies alone [134, 135].

It remains uncertain whether a negative mpMRI can justify omitting biopsy because of the heterogeneity and potential selection bias of published studies [122, 127]. It is therefore not possible to recommend using targeted biopsies only [3].

Multiparametric MRI remains limited by its inter-reader variability and the heterogeneity in definitions of positive and negative examinations. The first version of the Prostate Imaging Reporting and DataSystem (PIRADS) scoring system [136] failed to improve inter-reader interpretation as compared to subjective scoring [137, 138]. An updated version (PIRADS V2) has been proposed recently but needs to be evaluated further [139].

5.2.4.3   Guidelines for imaging

Recommendation	LE	GR
Before repeat biopsy, perform 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

mpMRI = multiparametric magnetic resonance imaging.

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 PCa detection rate [140]. 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 [141, 142]. To optimise detection of small lesions, paraffin blocks should be cut at three levels [112] 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 [143-145]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [143]. Table 5.2.4 lists the recommended terminology for reporting prostate biopsies [141].

Table 5.2.4: Recommended terminology for reporting prostate biopsies [141]

Benign/negative for malignancy. If appropriate, include a description.
Active inflammation
Granulomatous inflammation
High-grade 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

PIN = prostatic intraepithelial neoplasia.

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 2005 Gleason score (i.e., 2005 ISUP Modified Gleason System) [31]. A global Gleason score comprising all biopsies is also reported as well as the ISUP 2014 grade group (see Section 4.2). Intraductal carcinoma, lymphovascular invasion and extraprostatic extension must each be reported, if identified.

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 [146-148]. 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 [149]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [150] 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:
- 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: extraprostatic extension, seminal vesicle invasion, lymphovascular invasion, intraductal carcinoma, peri-neural invasion;
- ISUP 2014 grade group (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 [151]. 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 [152].

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 [153]. 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 [31]. 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

Recommendation	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   RP specimen report
The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.2.5). As a result of the complex information provided on each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.2.6). Synoptic reporting results in more transparent and complete pathology reporting [154].

Table 5.2.5: 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, presence of bladder neck invasion, laterality of extraprostatic extension 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 5.2.6: Example checklist: reporting of prostatectomy specimens

Histopathological type
• Type of carcinoma, e.g. conventional acinar, or ductal
Histological grade
•   Primary (predominant) grade
•   Secondary grade
•   Tertiary grade (if applicable)
•   Global Gleason score / ISUP 2014 grade group
•   Approximate percentage of Gleason grade 4 or 5
Tumour quantitation (optional)
•   Percentage of prostate involved
•   Size/volume of dominant tumour nodule
Pathological staging (pTNM)
If extraprostatic extension is present:
o   indicate whether it is focal or extensive
o   specify sites
o   Indicate whether there is seminal vesicle invasion
If applicable, regional lymph nodes:
o   location
o   number of nodes retrieved
o   number of nodes involved

Surgical margins
If carcinoma is present at the margin:
o   specify sites
Other
•   Presence of lymphovascular / angio-invasion
•   Location of dominant tumour
•   Presence of intraductal carcinoma

5.2.6.2.1   Gleason score in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2005 modified) Gleason system [31] is the strongest prognostic factor for clinical behaviour and treatment response. The Gleason score is incorporated in nomograms that predict disease-specific survival after prostatectomy [155].

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 ≤ 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 [156] 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 extraprostatic extension. It is useful to report the location and extent of extraprostatic extension because the latter is related to recurrence risk [157].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive extraprostatic extension. Some describe focal as a few glands [158] or extension as < 1 high-power field (HPF) [159], whereas others measure the depth of extent in millimetres [160].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute extraprostatic extension. 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 [161, 162] and should be recorded as extraprostatic extension (pT3a). A positive margin at the bladder neck should be reported as extraprostatic extension (pT3a) with positive margin, and not as pT4.

Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [163].

5.2.6.3   *PCa volume*

The independent prognostic value of PCa volume in RP specimens has not been established [159, 164-167]. Nevertheless, a cut-off of 0.5 mL is commonly used to distinguish insignificant from clinically relevant cancer [164]. 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 [168].

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 [165] 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 [169].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of extraprostatic extension [170]. There is insufficient evidence to prove a relationship between margin extent and recurrence risk [159]. 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 [171], or number of blocks with positive margin involvement.

5.2.7   *Guidelines for the clinical diagnosis of PCa*

Recommendation	LE	GR
Do not use transurethral resection of the prostate as a tool for cancer detection.	2a	A
Use the ISUP 2005 modified Gleason grading system for grading of PCa.	2a	A
Base the decision to perform a biopsy on PSA testing and 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. PHI, 4Kscore or PCA3] 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 10-12 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 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

DRE = digital rectal examination; ISUP = International Society of Urological Pathology; PCa = prostate cancer; PCA3 = prostate cancer gene 3; PHI = Prostate Health Index; PSA = prostate-specific antigen.

5.3   Diagnosis: Clinical staging
The extent of PCa is evaluated by DRE and PSA, and may be supplemented with bone scanning and 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. DRE is positively correlated with tumour stage in < 50% of cases [172], 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. Prostate specific antigen is produced by benign and malignant tissue, thus, there is no direct relationship between serum PSA and clinicopathological tumour stage [173]. In prostate needle biopsy, the percentage of cancerous tissue is a strong predictor of positive surgical margins, SVI, and non-organ-confined disease [174]. An increase in tumour-positive biopsies is an independent predictor of extraprostatic extension, margin involvement, and lymph node invasion [175]. Serum PSA, Gleason score, and T stage are more useful together than alone in predicting final pathological stage [155, 176]. These models may help to select candidates for nerve-sparing surgery and lymphadenectomy (Section 7.2).
    Seminal vesicle invasion is predictive of local relapse and distant metastatic failure. Seminal vesicle biopsies can improve pre-operative staging accuracy [177]. This is not recommended for first-line examination, but is 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 [178, 179]. Patients with positive biopsies from the base of the prostate are more likely to have positive SV biopsies [180].
    Transperineal 3D prostate mapping biopsy (PMB) is an alternative to transrectal biopsies because it provides more accurate tumour localisation, extent and Gleason grading [181], and has acceptable morbidity.

5.3.1.3   *Transrectal ultrasound (TRUS)*
Transrectal ultrasound is no more accurate at predicting organ-confined disease than DRE [182, 183].

Combined DRE and TRUS can detect T3a PCa more accurately than either method alone [184]. Even 3D-TRUS, colour Doppler and contrast agents may help in local staging [185, 186], but all TRUS techniques are largely operator-dependent and cannot differentiate between T2 and T3 tumours with sufficient accuracy to be recommended for routine staging.

5.3.1.4 *Multiparametric magnetic resonance imaging (mpMRI)*
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 extracapsular extension (ECE), SVI, and overall stage T3 detection showed 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 [187]. Multiparametric magnetic resonance imaging has poor sensitivity since it cannot detect microscopic extraprostatic extension. Its sensitivity increases with the radius of extension within periprostatic fat. In one study, the ECE detection rate increased from 14 to 100% when the radius of extension increased from < 1 mm to > 3 mm [188]. In another study, mpMRI sensitivity, specificity and accuracy for detecting pT3 stage were, 40, 95 and 76%, respectively, for focal (i.e. microscopic) extraprostatic extension, and 62, 95 and 88% for extensive extraprostatic extension [189].

The use of high field (3T) or functional imaging in addition to T2-weighted imaging improves sensitivity for ECE or SVI detection, but the experience of the reader remains of paramount importance [190]. Magnetic resonance imaging, although not perfect for local staging, may improve prediction of the pathological stage when combined with clinical data [191, 192].

Given its low sensitivity for focal (microscopic) extraprostatic extension, mpMRI is not recommended for local staging in low-risk patients [191, 193, 194]. However, mpMRI can still be useful for treatment planning in selected low-risk patients (e.g. candidates for brachytherapy) [195].

5.3.2 **N-staging**
5.3.2.1 *PSA level and biopsy findings*
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 [155, 196, 197]. Measurement of PSA alone is unhelpful in predicting lymph node metastases. Nomograms or Partin tables can define patients at low risk (< 10%) of nodal metastasis, although nomograms may be more accurate in establishing the extent of nodal involvement [176, 198]. The simple Roach formula can also be used [199]. Patients with low- and intermediate-risk PCa may be spared N-staging before potentially curative treatment [155].

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 [200].

5.3.2.2 *Nodal staging using computed tomography and multiparametric magnetic resonance imaging*
Abdominal CT and mpMRI indirectly assess nodal invasion by measuring lymph node diameter. Their sensitivity is low and microscopic invasion cannot be detected. Using a 10-mm threshold, CT or mpMR sensitivity is < 40% [201-213]. Among 4,264 patients, 654 (15.3%) had positive lymph nodes at lymphadenectomy but only 105 (2.5%) had a positive CT scan. Median estimated CT sensitivity, specificity, NPV and PPV were 7%, 100%, 85% and 100%, respectively [212].

Fine-needle aspiration biopsy (FNAB) may be useful in cases with positive imaging, even if it has a false-negative rate of 40% [214].

For CT or mpMRI, detection of microscopic lymph node invasion is < 1% in patients with a Gleason score < 8, PSA < 20 ng/mL, or localised disease [209, 215, 216]. Computed tomography and mpMRI should not be used for nodal staging in low-risk patients and be reserved for high-risk cancer.

5.3.2.3 *Lymphadenectomy*
The currently available most optimal method for N-staging is open or laparoscopic lymphadenectomy (see Section 7.2.6).

Primary removal of sentinel lymph nodes aims to improve accuracy of detecting tumour bearing nodes while reducing morbidity associated with extended pelvic lymph node dissection (LND) [217, 218]. Image guidance allows intraoperative sentinel node (SN) detection visually [219]. Difficulty in accessing the SN and the lack of data from large multicentre cohorts are major limitations of this technique. Therefore, for the time being, this remains experimental [220].

5.3.3   M-staging
5.3.3.1   Bone scan
Bone scan (BS) has been the most widely used method for evaluating bone metastases of PCa. However, it suffers from relatively low specificity [221]. Thus, in patients with equivocal findings, the lesions need to be assessed by other imaging modalities.

The NPV for bone scanning is 87-100% [214, 222-230]. Its diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour Gleason score [222-235] and these three factors were the only independent predictors of BS positivity in a study of 853 patients [236]. The BS positivity rate is extremely low (< 1%) in low-risk patients [235, 237-239]. In contrast, it is 6.6 - 38.5% in patients with a PSA level of 20-50 ng/mL [222, 225-228, 230, 231, 237-239], 19 - 90.7% in patients with stage > T3 [222, 226, 228, 229, 231, 237] and 16.9 - 29.6% in patients with Gleason > 8 tumours [233, 234, 237, 239]. The proportion of positive BSs in patients with PSA levels of 10 - 20 ng/mL (1-33.3%) or Gleason 7 (2.8 - 22%) is quite variable from one study to another [214, 222, 223, 225-229, 238-240]. In two studies, a major Gleason pattern of 4 was found to be a significant predictor of positive BS [238, 240].

Bone scanning should be performed in symptomatic patients, independent of PSA level, Gleason score or clinical stage [212].

5.3.4   New imaging modalities
5.3.4.1   Nodal metastases
[11]C- or [18]F-choline positron emission tomography (PET)/CT have good specificity for lymph node metastases, but a sensitivity of between 10-73% [241, 242].

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic lymph node metastases were 62% (95% CI: 51 - 66%) and 92% (95% CI: 89 - 94%), respectively [243]. 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 [244].

Therefore, choline PET/CT has no place for up-front staging in nodal metastasis. Currently, prostate-specific membrane antigen-PET CT (PSMA PET/CT) remains investigational.

Magnetic resonance imaging sensitivity is low for lymph node metastases and similar [245, 246] or inferior [247] to that of choline PET/CT.

5.3.4.2   Bone metastasis
[18]F-fluoride PET or PET/CT shows similar specificity and superior sensitivity to bone scanning [241, 248-252]. However, unlike choline PET/CT, it does not detect lymph nodes metastases, and it is less cost-effective compared to bone scanning [252].

It remains unclear whether [11]C-choline PET/CT is more sensitive than conventional bone scanning, but it has higher specificity, with fewer indeterminate bone lesions [241, 243, 253].

Diffusion-weighted whole-body and axial MRI are more sensitive than bone scanning and targeted radiography in detecting bone metastases in high-risk PCa [254-256]. Whole-body mpMRI is also more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [257]. A recent meta-analysis found that mpMRI 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) [258].

Table 5.3.1   Sensitivity and specificity for detecting bone metastases on a per-patient basis [258]

	Sensitivity%	Specificity%	CI
Bone Modality scan	78	85	95% (0.73-0.83)
PET	91	99	95% (0.83-0.96)
mpMRI	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, these techniques are currently limited by their lack of availability. The clinical benefit of detecting bone metastases at an earlier time-point using more sensitive techniques also remains unclear in the initial staging setting. Bone scan is therefore usually preferred in most centres.

Any risk group staging	LE	GR
Do not use CT and TRUS 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, metastatic screening, include at least a cross-sectional abdominopelvic imaging and a CT/MRI and bone-scan for staging purposes.	2a	A*
In predominantly Gleason pattern 4, use prostate mpMRI for local staging and metastatic screening.	2b	A

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

Upgraded following panel consensus.
CT = computed tomography; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PET = positron emission tomography; TRUS = transrectal ultrasound.

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 [259] and 45% of them are candidates for deferred management. There are two distinct strategies for conservative management that aim to reduce over-treatment: AS and watchful waiting (WW) (Table 7.1.1).

6.1.1.1   Definition
6.1.1.1.1   Active surveillance
Active surveillance aims to achieve correct timing for curative treatment, rather than delayed application of palliative treatment [260]. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening disease, 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 [259]

	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	Only for 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 15 years follow-up [259].

6.1.2.1   Active surveillance
The aim is to reduce over-treatment in patients with clinically confined, very-low-risk PCa, without compromising curative treatment [260]. Active surveillance is only proposed for highly selected low-risk patients. Current data are from ongoing prospective or retrospective cohorts, without any available RCTs.

One of the largest cohorts with the longest follow-up in a mainly low-risk population includes 993 patients (mean age: 67.8 years) [261]. These men presented with stage T1c or T2a PCa and PSA $\leq$ 10 ng/mL, age $\leq$ 70 years and a Gleason score $\leq$ 6 or age > 70 years with a score of $\leq$ 7. Initially, six biopsies were performed, but in recent years the 12-core protocol was introduced. After a median follow-up of 6.4 years (21% followed for more than 10 years), the 10- and 15-year OS were 80% and 62%, respectively. At 10 and 15 years, disease-specific survival (DSS) rates were 98.1% and 94.3%, respectively. Twenty-eight men (2.8%) developed metastases during follow-up (all but 2 being Gleason $\geq$ 7), and 15 died. Sixty-three and-a-half percent and 55% of men were still alive on AS at 10 and 15 years, respectively. Twenty-seven percent of this cohort eventually underwent radical treatment, prompted by a PSA-DT < 3 years in (43.5%), a Gleason score progression on repeat biopsies (35%) and patient preference (6%).

Several studies have investigated AS in organ-confined disease, the findings of which were summarised in a systematic review including > 3,900 patients [262]. There is considerable variation between studies regarding patient selection, follow-up policies and when active treatment should be instigated.

Selection criteria for AS published so far [262, 263] include: Gleason 6, when specified, < 2 - 3 positive cores with < 50% cancer involvement of every positive core, a clinical T1c or T2a, a PSA < 10 ng/mL and a PSA density < 0.15 ng/mL/cc. The later threshold remains controversial [263, 264]. A consensus meeting 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, extraprostatic extension or lymphovascular invasion in needle biopsy [265]. Some studies enrolled men with a PSA < 20 ng/mL, or up to T2b PCa, as well as men with a Gleason score 7 (3 + 4), a PSA < 10 ng/mL, a PSAD < 0.15 ng/mL/g, a T1c, and < 2 positive cores [266, 267]. These latter criteria are, as yet, not considered acceptable for an AS strategy, and should therefore not be used. A comprehensive review of the currently available patient selection- and follow-up criteria has been published [263].
        Biological markers, including urine PCA3, transmembrane protease, serine 2 - ETS-related gene (TMPRSS2-ERG) fusion, or PSA isoforms such as the PHI index appear promising as does genomics on the tissue sample itself [268-270]. However, further study data will be needed before such markers can be used in standard clinical practice. Re-biopsy to exclude sampling error is still considered standard practice, [263] even if this could be modified in the future [271] as re-biopsy is associated with increased rates of infectious complications [272].

Imaging with mpMRI is of particular interest due to its high NPV value for lesion upgrading and for staging anterior prostate lesions [273, 274]. A systematic review has been recently published [274] highlighting its important place in AS programmes.

Follow up in AS should be based on repeat biopsy, [263] serial PSA measurements and clinical examination (DRE). The optimal biopsy regimen is still unclear. As yet, mpMRI cannot replace follow-up biopsies and should not be used alone as an assessment tool to prompt active treatment [274].

The decision to suggest 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 the published cohorts. A PSA change (especially a PSA-DT < 3 years) is a less powerful indication for changed management based on its weak link with grade progression [275]. Active treatment may also be instigated upon a patient's request. This occurs in around 10% of patients on AS [276]. Overall, no major perturbation of health-related QoL and psychological well-being is apparent in the first years [277]. The same findings have been observed for WW [278].

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 *et al*, 2008 [279]	326	22	8/18 (44%)	98	100
Carter *et al*, 2007 [280]	407	41	10/49 (20%)	98	100
Adamy *et al*, 2011 [281]	533-1,000	48	4/24 (17%)	90	99
Soloway *et al*, 2010 [282]	99	45	0/2	100	100
Roemeling *et al*, 2007 [283]	278	41		89	100
Khatami *et al*, 2007 [284]	270	63		NR	100
Klotz *et al*, 2015 [261]	993	77	NR	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; 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 [285]. Watchful waiting is possible in patients with localised PCa and limited life expectancy.

Studies on WW have included patients with up to 25 years follow-up, with endpoints of OS and DSS. Several series have shown a consistent DSS rate of 82-87% at 10 years [286-291], and 80-95% for T1/T2 and Gleason score ≤ 7 [292]. In three studies with data beyond 15 years, the DSS was 80%, 79% and 58% [288, 290, 291], and two reported 20-year DSS rates of 57% and 32%, respectively [288, 290]. Of note is that these studies did not use the revised Gleason classification, which is associated with a slight increase in the grading. Practically, many patients classified as Gleason 6 in older studies would now be classified as Gleason 7. Therefore, the current Gleason 6 population has less aggressive disease compared to the patients classified in the above-mentioned cohorts.

Patients with well-, moderately- and poorly differentiated tumours had 10-year cancer-specific survival (CSS) rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis [292]. Observation was most effective in men aged 65-75 years with low-risk PCa [293].

In patients with stage cT1a PCa,10-year CSS rates were 96% and 94% for grade 1 and 2 tumours, respectively [286]. Metastasis-free survival (MFS) rate was 92% and 78% for patients with grade 1 and 2 tumours, respectively, indicating a higher risk of progression for moderately-differentiated tumours. Similar results were found in other studies of stage cT1a disease [294, 295].

Gleason 6-10 tumours carry a continuously increasing mortality risk up to 15 years follow-up after WW [296]. 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 6.1.4) [297, 298].

Table 6.1.4: 15-year mortality risk for localised PCa in relation to Gleason score in patients aged 55-74 years [297-299]

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 15 years.

Six hundred and ninety-five patients with T1/T2 PCa were randomised to WW or RP (Table 6.1.5) [299]. Although the study started after PSA screening was introduced, only 5% of men were diagnosed by screening.

After a median follow-up of 12.8 years, there was a significant decrease in cancer specific (CS) mortality, overall mortality, metastatic progression, and local progression in the RP group vs. the WW group.

Table 6.1.5: Outcome of Scandinavian Prostate Cancer Group Study Number 4 at 15 years follow-up [299]

	RP (*n* = 347) (%)	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)	nr

CI = confidence interval; nr = not reported; RP = radical prostatectomy.

The overall difference was not modified by PSA level (below or above 10 ng/mL) or Gleason score (below or above 7) at diagnosis. Age at randomisation had a profound impact, with a benefit in OS and MFS only in those aged < 65 years.

Another study randomised 731 men with clinically organ-confined PCa (PSA < 50 ng/mL and age < 75 years) to RP or WW [300]. Fifty percent of the patients had non-palpable PCa, compared to only 12% in the other trial [299]. Despite a 10-year life expectancy which was an inclusion criterion, > 33% of the men died within 10 years, suggesting that the population was less fit than expected, and reduced the ability to assess the survival benefit for active treatment [300].

After a mean follow-up of 10 years, there was no significant difference between the treatments for overall mortality (47% for RP vs. 49.9% for the WW group and PCa-specific survival, 5.8% for the RP group vs. 8.4% for the WW group). There were no significant differences in OS when considering patient age, Gleason score, performance status (PS), and Charlson comorbidity index (CCI) score. 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. There was a relative-risk and absolute-risk reduction of 31% and 10.5%, respectively, for patients with intermediate/high-risk PCa. Patients who underwent RP also had a significant reduction in bone metastases (4.7% vs. 10.6%).

Data from a 1995 study showed a tendency for a higher probability of metastases in the deferred treatment group and shorter CSS was reported after deferred therapy compared with immediate hormone therapy (HT) in presumed localised PCa after 15 years of follow-up [301]. Another study showed higher mortality in men with localised PCa treated with 150 mg/day bicalutamide compared with placebo [302].

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 [303]. Swedish data show a higher prevalence of deferred treatment in low-risk disease of 46% [304].

Many small, localised, well-differentiated tumours do not progress, and radical therapy may lead to substantial overtreatment. This was confirmed by a recent analysis at 5 and 10 years follow up in 19,639 patients aged > 65 years who were not given curative treatment. Most men with a comorbidity index score (CCI) score ≥ 2 died from competing causes at 10 years whatever their initial age. However, men without comorbidity or CCI score 1 had a low risk of death at 10 years, especially for well- or moderately differentiated lesions (Table 8.7) [305]. For CCI score ≥ 2, tumour aggressiveness had little impact on OS, suggesting that patients could have been spared biopsy and diagnosis of cancer. Thus, evaluation of initial comorbidity and survival probability before proposing biopsy or treatment is important [306].

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 [307]. Nine hundred and eighty-five patients with T0-4 N0-2 M0 PCa were treated with androgen-deprivation therapy (ADT) immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS hazard ratio (HR) was 1.21 (95% CI: 1.05-1.39), favouring immediate treatment. The time from randomisation to progression of hormone-refractory disease did not differ significantly, nor did CSS.

The median time to start of deferred treatment was 7 years. One hundred and twenty-six patients died without needing treatment (44% of deaths). Immediate ADT resulted in a modest but significant increase in OS, but no significant difference in PCa mortality or symptom-free survival, raising 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 ≤ 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 time to PSA relapse after response to immediate ADT correlated significantly with baseline PSA.

6.1.4   Deferred treatment for metastatic PCa (stage M1)
The only candidates for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side-effects. Median survival is ~2 years, 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 [308, 309]. Patients with deferred treatment for advanced PCa must be amenable to close follow-up.

6.1.5   Guidelines for active surveillance and watchful waiting

Recommendation - active surveillance	LE	GR
Discuss surgery and radiotherapy as treatment options with patients suitable for such treatments.	4	A*
Offer active surveillance to patients with the lowest risk of cancer progression: > 10 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
Follow-up should be based on DRE, PSA and repeated biopsies.	2a	A
Patients should be counselled on the possibility of needing further treatment in the future.	2a	A

Recommendation - 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

Recommendation - 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 ADT 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

Upgraded following panel consensus.
ADT = androgen-deprivation therapy; DRE = digital rectal examination; PSA = prostate-specific antigen.

6.2   Treatment: Radical prostatectomy
6.2.1   Introduction
Radical prostatectomy (RP) involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain negative margins. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. The goal of RP by any approach must be eradication of disease, while preserving continence and, whenever possible, potency [310]. Patients should not be denied this procedure on the grounds of age alone [306] but they should have at least 10 years of life expectancy. Increasing age is linked to increased incontinence risk (see Section 6.6). Increasing comorbidity greatly increases the risk of dying from non-PCa-related causes [305]. An estimation of life expectancy is paramount in counselling a patient about surgery [311] (see also Section 6.6 - Management of PCa in older men).

Currently, RP is the only treatment for localised PCa to show a benefit for OS and CSS, compared with WW, as shown in one prospective randomised trial [312]. The SPCG-4 trial showed that RP was associated with a reduction of all-cause mortality, with a relative risk (RR) of death at 18 years of 0.71 (95% CI: 0.59-0.86). The number needed to treat (NNT) to prevent one death at 18 years of follow-up was 8; it decreases to 4 for men younger than 65 years of age. Radical prostatectomy was also associated with a reduction in PCa-specific mortality (PCSM) at 18 years (RR: 0.56; 95% CI: 0.41-0.77). The benefit of surgery with respect to death from PCa was largest in men younger than 65 years (RR = 0.45) However, RP was also associated with a reduced risk of metastases among older men (RR = 0.68).

The benefits in OS and CSS were not reproduced in the overall study population (mean age 67 years) of another prospective randomised trial using the same methodology (PIVOT trial). After a median follow-up of 10 years, neither all-cause mortality (HR = 0.88; 95% CI: 0.71-1.08) or specific mortality (HR: 0.63; 95%

CI: 0.36-1.09) were reduced [300]. It must be highlighted that the populations included in these 2 RCTs are different, the SPCG trial includes a larger proportion of intermediate- or high-risk patients.

Robot-assisted laparoscopic prostatectomy (RALP) is displacing radical retropubic prostatectomy (RRP) as the most used surgical approach for clinically localised PCa in the USA and is being increasingly used in Europe and other parts of the world. This trend has occurred despite the lack of high-quality evidence to support the superiority of RALP. A recent systematic review demonstrated that robotic surgery had lower peri-operative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy, although there was considerable methodological uncertainty. There was no evidence of differences in urinary incontinence at 12 months and there was insufficient evidence to draw conclusions on differences in cancer-related, patient-driven or erectile dysfunction (ED) outcomes [313]. A recent, prospective, controlled, non-randomised trial of patients undergoing prostatectomy in 14 centres using RALP or RRP showed no difference in rates of positive surgical margins. At 12 months post-operatively, continence rates did not differ, but ED rates were significantly different with 70.4% after RALP and 74.7% after RRP [314].

Increased surgical experience has lowered the complication rates of RP and improved cancer cure [315-318]. 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 [319, 320]. More evidence for a volume-outcome relationship was provided by a recent systematic review [321].

There is a lack of studies comparing the different surgical modalities as well as of longer-term outcomes allowing comparison of more robust criteria, such as PCSM and overall mortality [313, 322-326]. Even though there appears to be a clear volume-outcome relationship, suggesting that referral of patients to high-volume centres would seem reasonable, the impact of a shift in practice has yet to be fully determined [321].

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 the balance of benefits and side effects of each therapy modality has been considered together with the patient.

6.2.2 Low-risk PCa

Patients with low-risk PCa should be informed about the results of two randomised trials comparing retropubic RP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.57 [95% CI: 0.40-0.81]) and distant metastases (RR: 0.40; 95% CI: 0.21-0.73) were significantly reduced in low-risk PCa at 18 years. However, death from PCa [RR: 0.54; 95% CI, 0.26-1.13]) was not reduced. In the PIVOT trial, a preplanned subgroup analysis of men with low-risk PCa showed that RP did not significantly reduce all-cause mortality (HR: 1.15; 95% CI: 0.80-1.66), or death from PCa (RR: 0.54; 95% CI: 0.26-1.13) at 10 years.

The decision to offer RP in cases of low-risk cancer should be based upon the probabilities of clinical progression, side-effects and potential benefit to survival [327]. It might therefore be reasonable to propose AS to selected patients whose tumours are most likely to be insignificant.

Apart from disease characteristics, age and comorbidities impact the choice for surgery vs. WW. Individual patient preferences should always be considered in shared decision making.

Extended pelvic lymph node dissection (eLND) is not necessary as the risk for pN+ does not exceed 5% [328].

6.2.3 Intermediate-risk, localised PCa

Patients with intermediate-risk PCa should be informed about the results of two randomised trials comparing RRP 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 18 years. In the PIVOT trial, according to a preplanned 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 10 years.

When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year PCSM rates of 13 and 19.6%, respectively [329].

The risk of having positive LNs in intermediate-risk PCa is between 3.7-20.1% [328]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [328]. In all other cases, eLND can be omitted, which means accepting a low risk of missing positive nodes.

6.2.3.1   Oncological results of radical prostatectomy in low- and intermediate-risk prostate cancer
Table 6.2.1 presents data from two prospective studies.

Table 6.2.1: Oncological results of radical prostatectomy in organ-confined disease

Study	Year of RP	Median follow-up (mo)	Risk category	12-year CSS (%)	18-year CSS (%)
Bill-Axelson *et al*, 2014 [312]	1989-1999	160	Low-risk		89.8
			Intermediate-risk		84.9
Wilt *et al*, 2012 [300]	1994-2002	120	Low-risk	100	
			Intermediate-risk	94.2	

CSS = cancer-specific survival; n = number of patients; 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 [330]. When managed with non-curative intent, high-risk PCa is associated with 10-year and 15-year PCSM rates of 28.8 and 35.5%, respectively [329].
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 lymph nodes is 15-40% [328].

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 Gleason 8-10 lesions. Patients with high-grade tumours confined to the prostate at histopathological examination have a good prognosis after RP. A high rate of downgrading exists between the biopsy Gleason score and the Gleason score of the resected specimen [331]. These men, in particular, may benefit most from potentially curative resection.
Several retrospective case series have demonstrated good outcomes after RP in the context of a multimodal approach (adjuvant or salvage ADT and/or RT) for patients with a biopsy Gleason score ≥ 8. Biochemical PFS (BPFS) at 5- and 10-years follow-up ranged between 35-51% and 24-39%, respectively, while the CSS at 5-, 10- and 15-years follow-up was 96%, 84-88% and 66%, respectively [331-334].

6.2.4.1.2   Prostate-specific antigen > 20 ng/mL
D'Amico *et al.* found that men with PSA levels > 20 ng/mL had a 50% risk of PSA failure at 5 years after RP [335]. Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multimodal approach demonstrated a BPFS at 5-, 10- and 15-years follow-up, ranging between 40-63%, 25-48% and 25%, respectively. The CSS at 5, 10 and 15 years ranged between 93-97%, 83-91% and 71-78%, respectively [333-338]. Spahn *et al.* published the largest multicentre surgical series to date, including 712 patients with PSA > 20 ng/mL, and reported a CSS of 90% and 85% at 10 and 15 years follow-up, respectively [336].

6.2.4.2   Locally advanced PCa
The surgical treatment of clinical stage T3 PCa has traditionally been discouraged [339], mainly because patients have an increased risk of positive surgical margins and lymph node metastases and/or distant relapse [340, 341].
In recent years, however, there has been a renewed interest in surgery for locally advanced PCa and several retrospective case series have been published [342-344]. In up to 50% of cases this is part of multimodality treatment.
Nomograms, including PSA level, stage and Gleason score, can be useful in predicting the pathological stage of disease [345, 346] and therefore help with patient selection. In expert centres, it has been shown that continence can be preserved in most cases, and in some cases, potency can also be preserved [347].
Retrospective case series demonstrated 5-, 10- and 15-year BPFS ranging between 45-62%, 43-51% and 38-49%, respectively. Cancer-specific survival at 5-, 10- and 15-years ranged between 90-99%, 85-92% and 62-84%, respectively. Five- and 10-year OS ranged between 90-96% and 76-77%, respectively [342-344, 346-350].

Only a limited number of cohort studies provided survival data for surgery of cT3b-T4 PCa. In these studies, the CSS was 88-92% at 5 years and 87-92% at 10 years, while the OS was 73-88% at 5 years and 65-71% at 10 years [351-353].

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 preoperative staging. cN+ was not a significant predictor of cancer-specific mortality (CSM) (p = 0.6) [354]. Due to the limited evidence, local treatment of cN+ patients, in association with a multimodal approach, should be discussed with patients on an individual basis.

6.2.5 Rationale for RP in patients with cN0 but pathologically confirmed lymph node invasion (pN1) PCa

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% [355, 356]. Furthermore, two retrospective observational studies have shown a dramatic improvement in CSS and OS in favour of completed RP vs. abandoned RP in patients who were found to be N+ at the time of surgery [357, 358]. This highlights the fact that frozen section should no longer be considered and supports the role of RP as an important component of multimodal strategies of pN+ PCa. These findings have been corroborated in a contemporary retrospective analysis [358]. Radical prostatectomy resulted in superior survival of patients with pN+ PCa after controlling for lymph node tumour burden and frozen sections of lymph nodes intraoperatively are no longer recommended [359].

Recent studies described survival outcomes after surgery in pN1 PCa, with 5-, 10- and 15-year CSS ranging from 84-95%, 51-86% and 45%, respectively. The OS at 5, 10 and 15 years ranged from 79-85%, 36-69% and 42%, respectively [237, 355-358, 360, 361].

6.2.6 Indication and extent of pelvic lymph node dissection

It is generally accepted that extended pelvic lymph node dissection (eLND) provides important information for prognosis which cannot be matched by any other currently available procedure [245].

The individual risk of finding positive lymph nodes can be estimated using preoperative nomograms. Only a few of these nomograms are based on eLND templates. A risk of nodal metastases over 5% (Briganti nomogram, MSKCC, or Roach nomogram) is an indication to perform nodal sampling by an extended nodal dissection [328, 362, 363].

6.2.6.1 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, 75% of all anatomical landing sites are cleared [364]. A recent prospective mapping study confirmed that a template including the external iliac, obturator and internal iliac areas was able to correctly stage 94% of patients. Nevertheless, in pN+ patients, this template was associated with a 24% incomplete clearance from positive nodes [244]. Adding the common iliac area and the presacral area decreased this risk to 3%. It is recommended that for each region the nodes should be sent in separate containers for histopathological analysis.

Sentinel node analysis

Sentinel node (SN) mapping studies have shown that aside from the obturator and external iliac lymph nodes, the prostate also drains to the presacral nodes and most commonly to the internal iliac nodes [244, 364]. Adding SN mapping to extended nodal dissection aids in directing dissection to nodes most likely to contain nodal metastases. Sentinal node mapping in PCa is still an experimental method and the optimal technology, radioactive or fluorescence tracers, or both, has not been determined yet [365] (see Section: 5.3.2.3).

6.2.6.2 Early complications

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparing extended vs. limited LND, three-fold higher complication rates have been reported by some authors [366].

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. Other authors have reported more acceptable complication rates [367]. Similar rates of lymphoceles have been observed in RARP series, however, in one subgroup analysis lymphoceles were more common in the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [368, 369]. Briganti *et al.*, [366] showed more complications after extended compared to limited LND. In 20% of men a complication was reported after eLND. Lymphoceles occurred in 10% of cases. Thromboembolic events occurred in less than 1% of cases.

6.2.6.3   Outcome of pN1
Prognostic indicators
The number of involved nodes [370], the tumour volume within the lymph node, and capsular perforation of the nodal metastases are predictors of early recurrence after prostatectomy for nodal metastasised PCa [371]. A lymph node density (defined as the percentage of positive lymph nodes in relation to the total number of analysed/removed lymph nodes) over 20% was found to be associated with poor prognosis [372].

Survival in pN1
Recent studies described survival outcomes after surgery in pN1 PCa, with 5-, 10- and 15-year CSS rates ranging from 84-95%, 51-86% and 45%, respectively. The OS at 5, 10 and 15 years ranged from 79-85%, 36-69% and 42%, respectively [237, 256-258, 293, 373, 374]. The number of removed nodes was correlated with disease specific survival in men with nodal metastases [237, 360, 370, 375-379]. In one population based study with a 10-year follow-up, patients undergoing excision of at least 10 nodes (node-negative patients) had a lower risk of PCa-specific death at 10 years than those who did not undergo lymphadenectomy [380]. In another series, it was demonstrated that a more extensive LND was associated with improvement in CSS in patients with lymph node invasion [370]. Retrospective findings suggest, but do not prove that men with nodal metastases may benefit from more extended nodal dissection. Better staging in men with a higher nodal yield may have resulted in the observed improved survival. Clinical recurrence (imaging confirmed) is observed in 33% of men after prostatectomy for lymph node metastasised PCa after a median follow up of 17 years [354].

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 10-year CSS rate of 80% [355, 356]. In patients who prove to be pN+ after RP, early adjuvant HT has been shown to significantly improve CSS and OS in a prospective randomised trial. However, this trial included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics. It is unclear whether early adjuvant HT should still be used in the present era of increased detection of microscopic involvement as a result of more frequently performed eLND. The benefits should be judged against the side effects of long-term HT. Follow-up of PSA and delaying the initiation of HT until PSA level rises is therefore an acceptable option in selected cases with < 2 microscopically involved lymph nodes in an extended nodal dissection.

Adjuvant radiotherapy
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 [361]. 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 lymph nodes) and GS 7-10 and pT3-4 or R1 as well as men with 3-4 positive nodes were more likely to benefit from RT after surgery [361]. In A SEER retrospective population-based analysis, adding RT to RP showed a non-significant trend to improved OS but not PCa-specific survival, but data on the extent of additional RT is lacking in this study [359]. No recommendations can be made on 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 that found a benefit for adding RT to androgen ablation in pN1 patients [361]. However the optimal field (prostatic fossa only or whole pelvis) remains unclear.

Adjuvant chemotherapy
The TAX3501 trial compared the role of leuprolide (18 months) with and without docetaxel (6 cycles) in men after prostatectomy for high-risk PCa. The trial ended prematurely due to poor accrual and overall only 19.7% of patients were found to have nodal metastases. Adjuvant chemotherapy after prostatectomy should only be considered in a clinical trial.

6.2.7 Guidelines for eLND in prostate cancer and pN+ patients

Recommendation	LE	GR
Do not perform LND in low-risk PCa.	2b	A
Perform an eLND 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 limited LND.	2a	A
Upon detection of nodal involvement during RP:		
• Offer adjuvant ADT for node-positive (pN+);	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 and ≤ 2 nodes show microscopic involvement with a PSA < 0.1 ng/mL and absence of extranodal extension.	2b	B

ADT = androgen deprivation therapy; eLND = extended lymph node dissection;
LND = lymph node dissection; PCa = prostate cancer; RP = radical prostatectomy.

6.2.8 Complications and functional outcomes of radical prostatectomy

The intra-and peri-operative complications of retropubic RP and RALP are listed in Table 6.2.2 [381] and section 7.8.3 - Radical prostatectomy.

Table 6.2.2: Intra-and peri-operative complications of retropubic RP and RALP (Adapted from [313])

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.

Post-operative incontinence and ED are common problems following surgery for PCa. A recent systematic review found that the mean continence rates at 12 months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP [326]. 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, nonrandomised trial of patients undergoing prostatectomy in 14 centres using RALP or RRP was published. At 12 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) [314].

6.2.9 Indications for nerve-sparing surgery

Nerve-sparing RP can be performed safely in most men with localised PCa [382, 383]. Clear contraindications are patients in whom there is a high risk of extracapsular disease, such as any cT2c or cT3 PCa, any GS > 7 on biopsy. An externally validated nomogram predicting side-specific extracapsular extension can help guide decision making [384, 385]. Multiparametric MRI might be helpful for 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.

The early use of phosphodiesterase-5 inhibitors in penile rehabilitation remains controversial. Placebo-controlled prospective studies have shown no benefit from daily early administration of vardenafil or sildenafil vs. on-demand vardenafil or sildenafil in the post-operative period [386, 387]. Conversely, another placebo-controlled prospective study has shown that sildenafil has a significant benefit on the return of normal spontaneous erections [388].

6.2.10 Guidelines for radical prostatectomy

Recommendation	LE	GR
Discuss AS and radiotherapy with suitable patients.	4	A*
Offer RP to patients with low- and intermediate-risk PCa and a life expectancy > 10 years.	1b	A
Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk of extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	2b	B
In intermediate- and high-risk disease, use multiparametric MRI as a decision tool to select patients for nerve-sparing procedures.	2b	B
Offer RP in a multimodality setting to patients with high-risk localised PCa and a life expectancy of > 10 years.	2a	A
Offer RP in a multimodality setting to selected patients with locally advanced (cT3a) PCa, and a life expectancy > 10 years.	2b	B
Offer RP in a multimodality setting to highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1).	3	C
Do not offer neoadjuvant hormonal therapy before RP.	1a	A
Do not offer adjuvant hormonal therapy for pN0.	1a	A
Offer any surgical approach (i.e. open, laparoscopic or robotic) to patients who are surgical candidates for radical prostatectomy.	1a	A

*Upgraded based on panel consensus
AS = active surveillance; DFS = disease-free survival; GS = Gleason score; MRI = magnetic resonance imaging; OS = overall survival; PCa = prostate cancer; RP = radical prostatectomy.

6.3 Treatment: definitive radiotherapy

6.3.1 Introduction
There are no published RCTs comparing RT with WW or AS. The only randomised trial in the modern era is the ProtecT study which has not yet reported its first results [389].

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold 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 [390]:
- 2009 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 [391]);
- 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 a 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 randomised trials 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 [392]. 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 randomised studies (see below) have shown that dose escalation (range 74-80 Gy) has a significant impact on 5-year survival without biochemical relapse [393-402]. 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 [403].

In everyday practice, a minimum dose of $\geq$ 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 III for the rectum is about 2-3% and for the genito-urinary tract is 2-5% [395, 402, 404-417] (see also Section 6.8.4.1 Post-treatment quality of life in patients with localised PCa).

Table 6.3.1: Randomised trials on dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up	Outcome	Results
MD Anderson study 2011 [393]	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 study [394]	393	T1b-T2b PSA 15 ng/mL 75% GLS < 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 Biochemical failure (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 study [390]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	Median 10 yr	Biochemical progression free survival (BFS); OS	43% BFS @ 64 Gy 55% BFS @ 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)
Dutch randomised phase III trial [402]	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 yrs	43% FFF @ 68 Gy 49% FFF @ 78 Gy (p = 0.045)
French GETUG 06 randomised trial [397]	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 [403] | 16,714 | intermediate risk 73% T ≤ 2a 76% GLS ≤ 7a | < 75.6 Gy vs. ≥ 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 ≥ 2b 67% GLS ≥ 7b | < 75.6 Gy vs. ≥ 75.6 Gy 77% HT | | | propensity adjusted HR: 0.82 favouring dose escalation (p < 0.001) |

BCF = biochemical failure; HT = hormone therapy; OS = overall survival.

6.3.3.2 *Hypofractionation (HFX)*

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 [400].

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 [401]. 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 [418-424]. A systematic review 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 [425]. 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 genito-urinary and rectal toxicity, and long-term side effects may not all be known yet [425-427].

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. For extreme HFX, it seems prudent to restrict this therapy to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Table 6.3.2: Phase 3 randomised trials of moderate hypofractionation for intact PCa

Study	n	Risk, GS, or NCCN	Regimen	BED, Gy	Median FU, mo	Outcome	Toxicity
Lukka et al. [418]	466	60% GS 6 31% GS 7 9% GS 8-10	52.5 Gy/20 fx	62	68	5 yr FFBF 40% (NS)	Gr ≥ 3 2% (NS)
	470		66 Gy/33 fx	66		5 yr FFBF 43%	Gr ≥ 3 1%
Yeoh et al. [419]	108	n.s.	55 Gy/20 fx	66.8	90	7.5 yr FFBF 53% (p < 0.05)	Late GU; HR: 1.58 (95% CI: 1.01-2.47) favouring hypofractionation
	109		64 Gy/32 fx	64		7.5 yr FFBF 34%	
Dearnaley et al. [420]	151	n.s.	57 Gy/19 fx	73.4	51	n.s.	Gr ≥ 2 GU 0% (NS) Gr ≥ 2 GI 1% (NS)
	153		60 Gy/20 fx	77			Gr ≥ 2 GU 2% Gr ≥ 2 GI 4%
	153		74 Gy/37 fx	74			Gr ≥ 2 GU 2% Gr ≥ 2 GI 4%
Kuban et al. [421]	102	29% low 70% intermediate 1% high	72 Gy/30 fx	80.2	56	5 yr FFBF 96% (NS)	5 yr Gr ≥ 2 GU 19% (NS)
	102		75.6 Gy/42 fx	71.4		5 yr FFBF 92%	5 yr Gr ≥ 2 GI 14% (NS) 5 yr Gr ≥ 2 GU 19% 5 yr Gr ≥ 2 GI 6%
Arcangeli et al. [422, 423]	83	26% GS 7 74% GS >7	62 Gy/20 fx	81.4	70	5 yr FFBF 85% (p = 0.065) *p ss for GS ≥ 4 + 3	3 yr Gr ≥ 2 GU 16% (NS) 3 yr Gr ≥ 2 GI 17% (NS)
	85		80 Gy/40 fx	80		5 yr FFBF 79%	3 yr Gr ≥ 2 GU 11% 3 yr Gr ≥ 2GI 14%
Pollack et al. [424]	151	34% GS 6 47% GS 7 19% GS 8-10	70.2 Gy/26 fx	84	68	5 yr BCDF 23% (NS)	5 yr Gr ≥ 2 GU 13% (p = 0.16) 5 yr Gr ≥ 2 GI 9% (NS)
	152		78 Gy/36 fx	78		5 yr BCDF 21%	5 yr Gr ≥ 2 GU 13% 5 yr Gr ≥ 2 GI 9%
Aluwini et al. [428]	403	30% GS ≤ 6 45% GS > 7 25% GS 8-10	64.6 Gy/19 fx	90.4	49	n.s.	3 mo. ≥ 2 GU 23% 3 mo. ≥ 2 GI 13%
	391		78 Gy/39 fx	78			3 mo. ≥ 2 GU 22% 3 mo. ≥ 2 GI 13%

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; CI = confidence interval; FFBF = freedom from biochemical failure; FU = follow-up; fx = fractions; GI = gastrointestinal; Gr = grade; GS = Gleason score; GU = genito-urinary; HR = hazard ratio; NCCN = National Comprehensive Cancer Network; NS = not significant; n.s. = not stated; ss = statistically significant.

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 randomised trials [429-433] (Table 7.3.3). 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 2 or 3 months before (for neoadjuvant), but the concomitant component is crucial to potentiate RT. Long-term ADT, ranging from 2 to 3 years is recommended for locally advanced disease [399, 434] rather than short term (6-months) [433]. Dose

escalation phase III randomised trials are on going to assess its impact on DFS. Cardiovascular mortality may be related to ADT, not RT, as addressed in Section 12.9.3.3.

Whether these results should be applied to patients with intermediate- or high-risk localised PCa is unclear. The Boston trial has shown an improved 8-year OS rate for patients without moderate or severe comorbidity assigned to 6 months of complete ADT (p = 0.01) [432], and the RTOG 94-08 study showed an increased 10-year OS rate for intermediate risk only with 4 months of complete ADT (p = 0.003) [398].

The EORTC trial 22961, an equivalence trial with 970 patients (78% T3-4, 92% N0) combined RT (70 Gy) with either 6 months or with 3 years of LHRH analogue treatment. With a median follow-up of 6.4 years, both cancer-specific and overall mortality were significantly lower with long-term androgen suppression [399].

In the RTOG 9910 trial, 1,579 intermediate-risk PCa patients were randomised to LHRH antagonist therapy for 8 weeks before RT (70.2 Gy in 2-D or 3-D techniques) followed by either another 8 or 28 weeks of anti-hormonal treatment. Extended androgen suppression did not significantly improve 10-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 [435].

Table 6.3.3: Studies of use and duration of ADT in combination with RT for PCa

Trial	Year	TNM stage	n	Trial	ADT	RT	Effect on OS
EORTC 22863 [429]	2010	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 10 years for combined treatment (HR: 0.60, 95% CI: 0.45-0.80, p = 0.0004).
RTOG 85-31 [430]	2005	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 Gleason score 7-10
Granfors [436]	2006	T3 N0-1 M0	91	EBRT ± ADT	Orchiectomy	65 Gy RT	Significant benefit (p = 0.02 p = 0.03), mainly caused by lymph-node-positive tumours
D'Amico [432]	2008	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 2011 [433]	2011	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 yrs: HR: 0.84, 0.65-1.08; p = 0.18)
RTOG 94-13 [437]	2007	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 [431]	2008	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 [434]	2008	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 Gleason score 8-10
EORTC 22961 [399]	2009	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yrs	70 Gy 3D-CRT	Better result with 3-year treatment than with 6 mo. (3.8% improvement in survival at 5 yr)
Pisansky [435]	2014	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 [438]	2014	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 [439, 440]	2015	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-years OS = 49% vs. 55% favouring combined treatment (HR: 0.7, p < 0.001)
Mottet 2012 [441]	2012	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-years OS 71.4% vs. 71.5%

LHRH = luteinising-hormone-releasing hormone; 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 progression-free survival (PFS) in a cohort of 413 high-risk patients. Patients were randomly assigned to either goserelin 10.8 mg every 3 months for 3 years, plus four cycles of docetaxel and estramustine or to goserelin alone (arm 2). Local therapy was administered at 3 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 3 months of treatment) was obtained in 34% in the ADT + DE arm and 15% in the ADT arm. With a median follow-up period of 4.6 years, the 4-year PFS was 85% in arm 1 vs. 81% in arm 2 (p = 0.26), but the data need to mature [442].

6.3.3.5   Combined dose-escalated radiotherapy and androgen-deprivation therapy

Zelefsky *et al.* [443] 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%). 3D-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 10 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 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before RT. The 10-year 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 6-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 (4-6 months) [398, 444, 445]. 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 [431, 432, 437], 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 lymph nodes). With a median follow-up time of 8 years, OS was significantly improved in the patients allocated to ADT + RT (HR:, 0.70; 95% CI: 0.57 to 0.85; p < 0.001). Deaths from PCa were significantly reduced by the addition of RT to ADT (HR: .46; 95% CI: 0.34 to 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 [440].

A total of 273 patients with locally advanced PCa T3-4 or pT3 N0 M0 were randomly assigned to 3 years of ADT using an LHRH agonist (leuprorelin), with or without RT (70 Gy to the prostate plus 48 ± 2 Gy to the pelvic lymph nodes). After a median follow-up period of 67 months, there was a significant improvement in the 5-year DFS (p < 0.001), metastatic disease-free survival (p < 0.018), and locoregional PFS (p < 0.0002), but the effect on OS was not reported [441].

Another study compared hormonal treatment alone (i.e. 3 months of continuous androgen blockade followed by continuous flutamide treatment (n = 439) with the same treatment combined with RT (n = 436) [438]. The 10 (15) year cumulative PCSM was 18.9% (30.7%) and 8.3% (12.4%) (HR: 0.35; [p < 4.1E-10 for 15 year results]), and overall mortality was 35.3% (56.7%) and 26.4% (43.4%) (HR: 0.70; p = 0.0006 for 15-year results), respectively.

6.3.3.7   Lymph node irradiation
6.3.3.7.1   Prophylactic lymph node irradiation in clinically N0 prostate cancer (estimated cN0)
There is no level 1 evidence for prophylactic whole-pelvic irradiation, since randomised trials have failed to show that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases. Such studies include the RTOG 77-06 study (n = 484 with T1b-T2) [446], the Stanford study (n = 91) [447], and the GETUG 01 trial (n = 444 with T1b-T3 N0 pNx M0) [448]. In the RTOG 94-13 study [437], 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

lymphadenectomy may be needed to improve the selection of patients who may be able to benefit from pelvic lymph node irradiation and to supplement the use of the Briganti tables [328] and/or the Roach formula [449]. The results of pelvic lymphadenectomy, 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 trails 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 randomised phase II in the UK, 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 [399], 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 5-year (54%) and 9-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 [450]. Patients with pelvic lymph node 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 STAMPEDE trial suggests that pelvic RT could be beneficial for N1 disease, but this is not based on a randomised comparison [451] (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 [452]; the other study suggested a clearer advantage for protons [453].

One randomised trial 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 [394]. 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 [454, 455], 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 [455].

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 [456].

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 brachytherapy for localised PCa*
There is a consensus on the following eligibility criteria for LDR monotherapy [457]
*   Stage cT1b-T2a N0, M0;
*   Gleason score 6 with ≤ 50% of biopsy cores involved with cancer or;
*   Gleason 3 + 4 score with ≤ 33% of biopsy cores involved with cancer;
*   An initial PSA level of ≤ 10 ng/mL;
*   A prostate volume of < 50 cm^3;
*   An International Prostatic Symptom Score (IPSS) ≤ 12.

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. Guidelines on the clinical and technical aspects of brachytherapy have been published and are strongly recommended [457-459]. There have been no randomised trials comparing brachytherapy as

monotherapy with other curative treatment modalities. Outcome data are available from a number of large population cohorts with mature follow-up [460-467]. The BDFS for Gleason 6 patients after 5 and 10 years has been reported to range from 71% to 93% and 65% to 85%, respectively [460-467].

A significant correlation has been shown between the implanted dose and recurrence rates [468]. 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 4 years than patients who received less than 140 Gy (92 vs. 68%). There is no benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [460].

Some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), post-implantation transurethral resection of the prostate (TURP), which is required in up to 8.7% of cases, and incontinence (0-19%) [469]. A small randomised trial has suggested that prophylactic tamsulosin does not reduce the rates of acute urinary retention, but may improve urinary morbidity [470]. 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 benign prostatic hyperplasia increases the risk of post-implantation incontinence and urinary morbidity.

Erectile dysfunction develops in about 40% of the patients after 3-5 years. In a retrospective analysis of 5,621 men who had undergone LDR monotherapy [471], the urinary, bowel, and erectile morbidity rates were 33.8%, 21%, and 16.7%, respectively, with invasive procedure rates of 10.3%, 0.8%, and 4%, respectively. A small randomised trial 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 [472].

LDR brachytherapy combined with EBRT for intermediate- and high-risk PCa
In cases of intermediate- or high-risk localised PCa, brachytherapy, supplemental EBRT [473] and neoadjuvant hormonal treatment [474] may be considered. Dose-escalated EBRT has been compared with EBRT followed by a LDR brachytherapy boost in intermediate-risk and high-risk patients in a randomised trial [475]. 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 full paper is pending.

6.3.5.2   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. Guidelines advising on clinical and technical issues are available and recommended [476]. High-dose-rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [477]. Higher doses of supplemental EBRT than this may best be delivered with IMRT [478].

Data suggest an equivalent outcome in terms of the BDFS in comparison with high-dose EBRT (HD-EBRT) [479]. In a retrospective analysis of modern series [463, 480], BDFS rates of 85.8%, 80.3% and 67.8% in men with low-risk, intermediate-risk, and high-risk PCa, respectively, were reported after a mean follow-up of 9.43 years. Quality-of-life changes are similar with high-dose EBRT and HDR brachytherapy in terms of diarrhoea and insomnia [481]. However, the frequency of ED was significantly increased with HDR brachytherapy (86 vs. 34%). A single randomised trial of EBRT vs. EBRT and HDR brachytherapy boost has been reported [482]. A total of 218 patients with organ-confined PCa were randomised to EBRT alone with a dose of 55 Gy in 20 fractions, or EBRT with a dose of 35.75 Gy in 13 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 5-, 7- and 10-year estimates of biochemical control 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-completed 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 2 years, possibly due to a dose lower than the current standard used [482]. A systematic review 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, randomised trial [483].

	Differences in prostate brachytherapy techniques
Low Dose Rate (LDR)	• 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)	• 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

6.3.5.3   Side effects of percutaneous irradiation and brachytherapy
Radiotherapy affects erectile function to a lesser degree than surgery, according to retrospective surveys of patients [484]. A meta-analysis has shown that the 1-year probability rates for maintaining erectile function were 0.76 after brachytherapy, 0.60 after brachytherapy + external irradiation, 0.55 after external irradiation, 0.34 after nerve-sparing RP, and 0.25 after standard RP. When studies with more than 2 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 [485].

Studies have demonstrated a significantly increased risk of developing secondary malignancies of the rectum and bladder following EBRT [486, 487]. 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 [486]. Another analysis [487] 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 [488]. 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 10 years [489]. 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 [489].

*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 5 years [490]. Three prospective randomised trials have assessed the role of immediate post-operative RT (adjuvant RT [ART]), as follows:

6.3.6.1   EORTC 22911
EORTC 22911 [491], 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 RRP. Grade 4 toxicity was not observed (Criteria: see Tables 6.8.1 and 6.8.2). The rate of grade 3 GU toxicity was 5.3% vs. 2.5% in the observation group after 10 years. For patients younger than 70 years, the study concluded that immediate post-operative RT after surgery significantly improved the 10-year biological PFS to 60.6% vs. 41.1% in the observation group. Loco-regional control was better in the long-term follow-up at 10 years after immediate irradiation (HR: 0.45; p < 0.0001). However, ART patients with pT2-3 R1 also showed an improved clinical PFS after 10 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 5 years for pT3 with negative margins and other risk factors [491].

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 [492].

6.3.6.3   SWOG 8794 trial
Conversely, the updated results, with a median follow-up of more than 12 years, of the SWOG 8794 trial, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, p = 0.016) and a 10-year OS of 74% vs. 66% (median: 1.9 years prolongation; p = 0.023) [493, 494].

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 [491, 492, 494] after recovery of urinary function;
or
•   Clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [495, 496] (see Section 6.10.5.1).

Table 6.3.4: Overview of all three randomised trials for adjuvant radiation therapy after RP*

Reference	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median follow-up (mo)	Biochemical Progression-free survival (bNED)	Overall survival
SWOG 8794 [494]	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 [491]	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 [492]	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; NS = not significant; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin.

6.3.7   Immediate (adjuvant) post-operative external irradiation after radical prostatectomy (pN1)
In a retrospective matched-pair analysis with 364 pN+ patients, men who received adjuvant RT in addition to ADT after RP had a 16% better 10-year CSS as compared to those without ADT [497]. In a recent study comparing lymph node positive prostatectomy patients who received either adjuvant ADT alone (n = 721) or ADT + ART (n = 386), the multimodal treatment reduced 8-year PCSM (13.8% vs. 7.6%, p = 0.08) [361]. Subgroup analysis in this retrospective study demonstrated a significant benefit from additional ART for patients with intermediate risk (1-2 positive nodes, GLS 7-10 and pT3b/4 or positive surgical margins; 6.9% vs. 15.8%, p = 0.03) and for patients with high risk (3-4 positive nodes irrespective of further risk parameters; 3.5% vs. 21.2%, p = 0.02). The results could be confirmed with the end-point OS. These data need prospective validation, but could be helpful in individual decision making.

Summary of evidence	LE
The highest effect of adjuvant radiotherapy is seen in patients with pT3R1 PCa.	1a

Recommendation	LE	GR
Discuss AS and surgery with all patients who would be suitable for these treatment options.	4	A
Offer EBRT to all risk groups of non-metastatic PCa.	2a	A
In low-risk PCa, use a total dose of 74 to 78 Gy.	1a	A
In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, offer LDR brachytherapy.	2a	A
In intermediate- risk PCa use a total dose of 76-78 Gy, in combination with short-term ADT (4-6 months).	1b	A
In patients with high-risk localised PCa, use a total dose of 76-78 Gy in combination with long-term ADT (2-3 years).	1b	A
In patients with locally advanced cN0 PCa, offer radiotherapy in combination with long-term ADT (2-3 years).	1a	A
Offer IMRT for definitive treatment of PCa by EBRT.	2a	A
In patients with cN+ PCa offer pelvic external irradiation in combination with immediate long-term ADT.	2b	B
In patients with pT3,N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it improves at least biochemical-free survival.	1a	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 (see Section 6.10.5.1).	2b	A

ADT = androgen deprivation therapy; AS = active surveillance; CRT = conformal radiotherapy;
EBRT = external-beam radiation therapy; IMRT = intensity-modulated radiotherapy; IPSS = International
Prostate Symptom Score; PCa = prostate cancer; PSA = prostate-specific antigen; TURP = transurethral
resection of prostate; WHO = World Health Organization.

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 [498-501]. In this Section, we will consider both whole gland and focal treatment, looking particularly at high-intensity focused US (HIFU) and cryosurgery (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 [498-501].

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.

Patients who are potential candidates for CSAP are those who have organ-confined PCa and those identified

as having minimal tumour extension beyond the prostate [498-500]. The prostate should be < 40 mL in size. Prostate glands > 40 mL should be hormonally downsized to avoid any technical difficulty in placing cryoprobes under the pubic arch. Prostate-specific antigen serum levels should be < 20 ng/mL, and the biopsy Gleason score should be < 7. Potential candidates for CSAP are:
- 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.

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 beyond 10 years.

6.4.2.1   Results of cryosurgery for PCa
A comparative assessment of primary ablative therapies for localised PCa, including CSAP, was recently undertaken [502]. The systematic review and network meta-analysis compared CSAP vs. RP and EBRT. Data from 3,995 patients across 19 studies (including 1 RCT, 4 non-randomised comparative studies, and 14 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 1-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 studies, the findings in relation to cancer-specific outcomes were considered inconclusive. The review noted significant inconsistencies in outcome definition, measurement and reporting in the evidence base, in particular biochemical recurrence.

In Ramsay *et al.*'s systematic review and meta-analysis [502], there was evidence that the rate of urinary incontinence at 1 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 for urinary incontinence at 1 year. CSAP had a numerically lower rate of ED at 1 year compared with RP but this was not statistically significant. 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.

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 [503]. 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. The procedure is time-consuming, with about 10 g prostate tissue treated per hour. Potential candidates are patients with low-to-moderate risk in investigational settings. 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 [504]. As a consequence of the lower PSA cut-off for recurrence than in the Phoenix criteria (PSA nadir + 2 ng/mL), the outcome may be approximately 10% lower using the Stuttgart criteria than the Phoenix criteria [505].

A recent systematic review and comparative assessment by network meta-analysis [502] compared HIFU vs. RP and EBRT as primary treatment for localised PCa. Data from 4,000 patients across 21 studies (including 1 non-randomised comparative study and 20 case series) were included.
There was some evidence that BCF rates were significantly higher at 1 year with HIFU than with EBRT. However, the difference was no longer statistically significant at 5 years. Similar statistically significant findings were observed with regard to DFS at 1 year, with worse outcomes for HIFU than for EBRT. The differences were no longer significant at 3 years. The biochemical result was in contrast to OS at 4 years, which was higher when using HIFU. In terms of toxicity, there were insufficient data on urinary incontinence, ED or bowel dysfunction to draw any conclusions, although at 1 year HIFU had lower statistically significant incontinence rates than RP. The safety profile for HIFU was generally good, apart from a potential numerical increase in rates of urinary retention and dysuria. 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.

In an earlier systematic review and meta-analysis [506], 150 papers related to HIFU were identified and evaluated with regard to various oncological and functional outcome parameters [506]. No controlled trial 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 [507-509]. 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 [510-512].

6.4.4.1 Pre-therapeutic assessment of patients

The high number of random and systematic errors associated with TRUS-guided random biopsy regimens mean that this procedure is not sufficiently accurate for selecting candidates for focal therapy. Transperineal biopsy or MRI may be useful tools. For characterising men considering focal therapy, transperineal prostate biopsy using a template-guided approach is recommended [513-515]. When used with a 5 mm sampling frame, this approach can rule in or out PCa foci with volumes of 0.5 mL and 0.2 mL with 90% certainty [516]. Thus, the exact anatomical localisation of the index lesion - defined as the biologically most aggressive - can be accurately determined.

6.4.4.2 Patient selection for focal therapy

The primary objective of treatment must be the eradication of measurable and biologically aggressive disease with minimal toxicity. However, although treatment is usually intended to be a single session, re-treatment may be necessary. There are no standardised follow-up schedules and re-treatment indications. Based on published data, the following criteria identify possible candidates for currently ongoing trials of focal treatment:
- candidates for focal therapy should ideally undergo transperineal template mapping biopsies; mpMRI with or without TRUS biopsy may be an option in experienced hands;
- focal therapy should be limited to patients with a low to moderate risk in investigational settings;
- retrospective data have shown the presence of grade I-III toxicity in 13% of cases [517];
- patients should be counselled and cautioned that no data on functional and oncological outcomes are available;
    1. the therapy is investigational;
    2. the long-term consequences are unknown;
    3. the optimal method for follow-up and the criteria for salvage therapy are not clear;
    4. focal therapy is not without toxicity.

Early reports suggest the feasibility of MRI-guided focal salvage cryotherapy after local RT [518] and focal electroporation [519].

6.4.4.3 Results of focal therapy for localised PCa

Ramsay et al.'s [502] systematic review 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 (5 studies reporting on focal CSAP, 3 studies on focal HIFU, and 1 study reporting on both). For focal CSAP vs. RP or EBRT, no statistically significant differences were found for BCR at 3 years. The incontinence rates at 1 year for focal CSAP were very low (< 1%), whilst the ED rate (range 0-40%) was similar to RP. Procedural complication rates were generally low, with the commonest complication being acute urinary retention (range 1.2-8.0%). For focal HIFU vs. RP or EBRT, there were no comparable data on oncological, continence nor potency outcomes at 1 year or more. The commonest reported complications were dysuria (22-30%), acute urinary retention (range 2-24%), urethral sloughing (up to 22%) and urinary tract infection (up to 17%).

6.4.5 Summary of evidence and guidelines for experimental therapeutic options to treat clinically localised PCa

Summary of evidence	LE
The available short-term data does not prove equivalence.	2b
There is no reliable long-term comparative data to indicate that CSAP or HIFU leads to equivalent oncological outcomes compared with radical prostatectomy or EBRT.	3
PSA nadir values after ablative therapies may have prognostic value.	3
Focal therapy of any sort appears promising but remains investigational, with uncertainties surrounding follow-up and re-treatment criteria.	3

Recommendation	LE	GR
Only offer cryotherapy and HIFU within a clinical trial setting.	3	B
Do not offer focal therapy of PCa as a therapeutic alternative outside clinical trials.	3	A

HIFU = high-intensity focused ultrasound.

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) [520].

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 [521]. 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 levels compared to 50 ng/dL [522-524]. 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 [525] and it is the quickest way to achieve a castration level which is usually reached within less than 12 hours. It is irreversible and does not allow for intermittent treatment.

6.5.3 Oestrogens

Treatment with oestrogens results in testosterone suppression but is not associated with bone loss [526]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side effects, especially thromboembolic complications, even at lower doses [527, 528] 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 2-3 days after adminstration and lasts for about 1 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 2-4 weeks

[529]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [530] and comparable to orchiectomy [531] [530].

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 [532].
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
Luteinizing-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.

6.5.5.1   Abarelix
Abarelix has shown to be equally effective as LHRH agonists in achieving and maintaining castration levels and in reducing serum PSA levels [533, 534]. However, the FDA issued a warning as regards allergic reactions with its long-term use, resulting in the suspension of its further development. It is still licensed in metastatic and symptomatic PCa, for which no other treatment option is available, or as a short-term induction modality (http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21320_plenaxis_lbl.pdf).

6.5.5.2   Degarelix
Degarelix is an LHRH antagonist with a monthly subcutaneous formulation. 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 3 [535]. An extended follow-up has been published, suggesting a better PFS compared to monthly leuprorelin [535]. 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 CPA) and hepatotoxicity.

6.5.6.1.1   Cyproterone acetate (CPA)
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 randomised trial [536] 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 [537]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.5.6.1.2   Megestrol acetate and medroxyprogesterone acetate
Very limited information is available, but these drugs are associated with a poor overall efficacy.

6.5.6.2   Non-steroidal anti-androgens
Non-steroidal anti-androgen monotherapy has been promoted on the basis of improved QoL compared to castration. Anti-androgens do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [538]. Non-androgen pharmacological side-effects differ between agents, with bicalutamide showing a more favourable safety and tolerability profile

than flutamide and nilutamide [539]. All three agents share a common potential liver toxicity (occasionally fatal) therefore, patients' liver enzymes must be monitored regularly.

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 5-6 hours, leading to a three times daily use. The recommended 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 [538, 540].

6.5.7   *New compounds (for castrate-resistant patients only)*
During castration, the occurrence of castration-resistance (CRPC) is systematic. It is considered to be mediated through two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent (see Section 6.11 - 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 adaptative mechanism [541]. 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 hydrolase 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 for relatively high costs. Furthermore, the greatest QoL gains and least costs may be obtained by starting ADT when symptoms from distant metastases have occurred [542]. 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 systematic review of ADT in PCa has recently been published [520].

6.6.2   *Prognostic factors*
Median survival of patients with newly diagnosed metastases is at least 42 months [543] 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 [544], alkaline phosphatase [545] 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 [546].

Based on a large SWOG 9346 cohort, PSA level after 7 months of ADT was used to create 3 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 13 months median survival [547]. This grouping, however, requires independent confirmation.

6.6.3 *First-line hormonal treatment*
Primary ADT has been the standard of care for the past decades [520]. 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 [548]. 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 4 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' per-se is unknown [549].

6.6.4 *Combination therapies*
6.6.4.1 *Complete androgen blockade (CAB)*
There are conflicting results from several studies comparing CAB with monotherapy. The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [550]. Systematic reviews 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) [551, 552] beyond 5 years of survival [553] 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 (NSAA) monotherapy*
Based on a Cochrane systematic review [554] 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 (IAD)*
Three independent reviews [555-557] and a meta-analysis [558] looked at the clinical efficacy of IAD. All of these reviews included eight RCTs of which only three were conducted in patients with M1 disease only. The five remaining trials included different patient groups, mainly locally advanced and metastatic patients relapsing.

So far, the SWOG 9346 [559] 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-analysis 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. 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 very recently published prospective trials came to the same conclusions [560, 561].

Other possible long-term benefits of IAD include bone protection [562] and a protective effect against metabolic syndrome. This possible protective effect has been challenged recently [563] and deserves more studies. Testosterone recovery was observed in most studies [564] leading to intermittent castration. Finally, IAD is associated with a very significant decrease in treatment costs. IAD is feasible and accepted by the patients [564].

The PSA threshold at which ADT must be stopped or resumed still needs to be defined in prospective studies [556, 564]. Nevertheless, there is consensus amongst authors on some statements:

- IAD is based on intermittent castration. Therefore, only drugs leading to castration are suitable.
- Most data has been published on CAB (rather than IAD).
- LHRH antagonist might be a valid alternative to an agonist.
- The induction cycle cannot be longer than 9 months, otherwise testosterone recovery is unlikely.
- ADT should be stopped only if patients have fulfilled all of the following criteria:
  - well-informed and compliant patient;
  - no clinical progression;
  - clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease.
- Strict follow-up is mandatory, with clinical examination every 3-6 months. The more advanced the disease, the closer the follow-up should be. The same laboratory should be used to measure PSA.
- Treatment is resumed when the patient progresses clinically, or has a PSA rising above a predetermined (empirically set) threshold: usually 10-20 ng/mL in metastatic patients.
- The same treatment is used for at least 3-6 months.
- Subsequent cycles of treatment are based on the same principles until the first sign of castration resistance become 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 [556].

IAD might be an option in patients with metastatic disease after a standardised induction period.

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. Current insights are mainly based on flawed, underpowered RCTs, with mixed patient populations (i.e. locally advanced, M1a, M1b status), and a variety of ADT treatments and follow-up schedules.

ADT was shown to be the most cost-effective therapy if started at the time the patient developed symptomatic metastases [542].

A Cochrane review extracted four good-quality RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [554]. 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 adjuvant after RP [565]. No improvement in OS was observed in the M1a/b population, although early ADT significantly reduced disease progression and associated complications.

The ASCO guidelines conclude that it is not possible to make a recommendation on when to start initial HT in advanced asymptomatic PCa [566]. The ESMO guidelines do not comment on this topic [567].

6.6.5   Hormonal treatment combined with chemotherapy

Three large RCT were conducted, two of which were fully published by September 2015 [546, 568]. The third and most recent trial presented initial findings at a conference [569]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks) (within 3 months of ADT initiation). The primary objective in all 3 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 months	Median OS (months)		HR	P value
				ADT + D	ADT		
Gravis [568]	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 [546]	M1 HV : 65%	790	28.9	57.6	44	0.61 (0.47-0.8)	< 0.001
STAMPEDE [569]	M1 [61%] / N+ [15%] / relapse	1,184 / 593 (D) 593 (D + ZA)		81 76	71 NR	0.78 (0.66-0.93) 0.82 (0.69-0.97)	0.006 0.022
	M1 only	725 + 362 (D)		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 4 bone metastases, with at least 1 outside the spine and pelvis; n = number of patients; ZA = zoledronic acid.

In the GETUG 15 trial [568], 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 [544]. In the 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 <u>four or more</u> bone metastases, with at least one outside the spine and pelvis [546].

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). Patients were included with either M1, or N1 or having 2 criteria out of three: T3/4, PSA ≥ 40 ng/mL, Gleason 8-10. Also relapsed patients after local treatment were included if they had one of the following criteria: PSA ≥ 4ng/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) [569, 571].

In the three trials toxicity was mainly haematologic 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 [572, 573].

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 [572]. Docetaxel is used at the standard regimen of 75mg/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 [574] and the Munich cancer registry [575] 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 6 months ADT and with ≤ 3 bone spots confirmed the feasibility and after a median 34 months follow up, suggested a better CSS [576]. 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 systematic review clearly highlighted that at this time this approach must, as yet, be considered as experimental [577].

6.6.8 *Guidelines for the first-line treatment of metastatic prostate cancer*

Treatment type	Modality	Recommendation	LE	GR
Castration combined with chemotherapy	Docetaxel combined with castration	Offer castration combined with chemotherapy to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.	1a	A
Castration alone	Surgical, LHRH agonist, OR LHRH antagonist	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
Castration combined with any local treatment	Radiotherapy/Surgery	Use castration combined with local treatment in an investigational setting only.	3	A

6.6.9 *Guidelines for hormonal treatment of metastatic prostate cancer*

Recommendation	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 an 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 7 days before the first LHRH analogue injection if patient has symptoms). Treat for four weeks.	3	A
Do <u>not</u> offer anti-androgen monotherapy in M1 patients.	1a	A
Intermittent treatment		
Population	In asymptomatic M1 patients, offer intermittent treatment to highly motivated men, with a major PSA response after the induction period.	1b	B
Threshold to start and stop ADT	• 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 6 to 7 months of treatment. • Resume treatment when the PSA level is > 10-20 ng/mL (or to the initial level if < 20 ng/mL).	4	C
Drugs	In M1 patients, offer combined treatment with LHRH agonists and NSAA.	1b	A
	Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction.	2	B

ADT = androgen deprivation therapy; LHRH = luteinising hormone-releasing hormone; NSAA = non-steroidal anti-androgen; PSA = prostate specific antigen.

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 [578]. A similar increase is expected in Europe [7].

The Surveillance, Epidemiology and End Results (SEER) database shows that 71% of PCa-related deaths occur in men aged ≥ 75 years [579], probably due to the higher incidence of advanced/metastatic disease [580-582].

Despite the high incidence and mortality rates in senior adults, they may be undertreated [583, 584]. 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 [585].

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 [305]. 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 [586]. This can be explained by the observations from a study in which patients did not receive active local treatment for their

PCa [305]. At 10 years, most men with a Charlson Comorbidity Index (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) [587] is the best tool for assessing mortality risk unrelated to PCa [588].

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
Vulnerable: one or two Grade 3 scores
Frail: > 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 [589-591]. 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 [592]. Nutritional status can be estimated from body weight during the previous 3 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 [593]. In patients undergoing major elective surgery, there is an association between baseline cognitive impairment and long-term post-operative complications and mortality [594]. Intervention is unlikely to reverse cognitive impairment, except in depression [66].

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 systematic evaluation of health status [66]. 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 [595].

Table 6.7.2: G8 screening tool (Adapted from [596])

	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
P	In comparison with other people of the same age, how does the patient consider his/her health status?	1 = no
		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**

G8 score > 14 shows that patients should receive the same treatment as younger patients. Patients with G8 ≤ 14 should undergo full geriatric evaluation, assessing comorbidity, nutritional status, and cognitive and physical functions, to determine if the impairment is reversible [596]. Patients with reversible impairment (vulnerable patients) should be treated according to EAU Guidelines. Patients with irreversible impairment (frail patients) should receive adapted treatment [66].

Table 6.7.3: Performance Scales - Karnofsky & ECOG Scores [595]

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 [66]. Patients with G8 score < 14 should undergo complete geriatric assessment to evaluate reversibility of any impairments [66].

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 vulnerable or frail). The treatment policy is then:
•   fit or healthy older men should receive standard treatment;
•   vulnerable patients may receive standard treatment after resolution of any geriatric problems;
•   frail patients should receive adapted treatment;
•   patients who are too sick with terminal illness should receive only palliative treatment [66].

After resolution of reversible impairments, a similar urological approach should be carried out in fit or vulnerable 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.

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 vulnerable patients (reversible impairment) after resolution of geriatric problems; 3. Offer adapted treatment to frail 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)

This topic 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 [597].

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 [580]. 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 (relative risk, 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) [312]. 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 [598, 599].

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 [600].

The drawback of associating ADT with EBRT in senior adults is discussed in Section 6.7. 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 [432].

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 [307, 601].

6.7.2.2   *Advanced PCa*

6.7.2.2.1   Hormone-naïve metastatic PCa

ADT 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 [66].

Routine bisphosphonates or denosumab to prevent skeletal complications in ADT is not recommended, unless there is a risk of fracture [602].

6.7.2.2.2   Metastatic CRPC

In metastatic CRPC, docetaxel is standard in fit and vulnerable older men [603], with comparable response and tolerance to younger patients [604]. Tolerability has not been specifically studied in frail older men. In elderly

and frail 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 [605-611].

Palliative treatment includes surgery, radiopharmaceuticals, EBRT, and medical treatment for pain and symptoms.

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 vulnerable patients (reversible impairment) after resolution of geriatric problems; 3. Offer adapted treatment to frail patients (irreversible impairment); 4. Offer only symptomatic palliative treatment to patients who are too sick with terminal illness.	B

Recommendation	LE	GR
Localised disease		
Offer standard treatment to fit and vulnerable 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 frail or 'too-sick' senior adults, offer immediate ADT only for symptom palliation.	1b	A
Offer minimally invasive energy-ablative therapies only to selected fit and vulnerable 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 vulnerable adults.	1b	B

ADT = androgen-deprivation therapy.

6.8 Side effects of local treatment and health-related quality of life in prostate cancer survivors

6.8.1 Introduction

The majority of PCa patients experience acute and late side effects of the disease and its treatment, which can be short term or long term, change in intensity over time and significantly impact their QoL. Increased life expectancy in PCa makes post-treatment QoL a key issue. Health-related QoL refers to the impact of disease and treatment on well-being, physical, emotional and social functioning, including daily functioning [612]. Health-related QoL is rated by patients, and is important because physicians often underestimate the impact of disease and treatment on patients [613].

Prostate cancer-specific HRQoL refers to the disease-specific outcome of PCa, including urinary, bowel and sexual functioning. General HRQoL refers to well-being, vitality, fatigue, pain, general health status, global QoL, and life satisfaction [614].

Health-related QoL is measured using standardised questionnaires, which provide an objective assessment of general and disease-specific domains [615, 616].

Comparison of the most common contemporary therapies for localised PCa is necessary to inform patients about treatment options and address patient preferences for the various possible outcomes. There is still limited objective data about HRQoL in PCa treatment.

6.8.2 Active surveillance and watchful waiting

Although AS and WW avoids treatment-related side effects, they carry an increased risk of psychological distress, which may significantly affect HRQoL [617].

In general, negative QoL effects remain limited in men with favourable clinical characteristics [618] [277]. Fear of disease progression and general anxiety decreased at 18 months of surveillance with only six of 129 men (5%) discontinuing AS because of anxiety and distress in the PRIAS study [619].

Risk factors for not doing well on AS include: patient perception that the physician is making

most of the decisions, poor physical health, high anxiety, high PSA, lack of a partner, neuroticism, mental impairment, recent diagnosis of PCa, lower number of core samples taken at diagnostic biopsy, and illness uncertainty. These factors are significantly associated with low HRQoL [620, 621] [622]. Interventions to reduce uncertainty and anxiety may enhance HRQoL for men with PCa on AS.

In contrast to AS, men managed with WW in the SPCG-4 trial were not followed closely to induce curative treatment if needed, which could explain the less favourable anxiety and depression scores compared to the PRIAS results [623].

A long-term comparison of WW and RP [623] found that depression, well-being and psychological status did not differ significantly among treatment groups over 8 years. However, men in the RP group reported more physical symptoms related to leakage, erection and libido.

Apart from psychological distress, untreated men may have a higher level of irritative/obstructive urinary symptoms compared to patients treated with RP or RT after 1-3 years [624].

6.8.3 *Radical prostatectomy*
Radical prostatectomy has a significant negative effect on multiple quality domains, including sexual and urinary function, and physical HRQoL [625-627]. In the PCa Outcomes Study (PCOS), at 2 years 8.7% of men had a lack of urinary control and 41.9% reported sexual dysfunction [628]. Recovery from sexual dysfunction and urinary incontinence occurs over 2-3 years [599, 629], with the latter being at its worst two months after surgery [625].

A recent systematic review found that the mean continence rates at 12 months were 89-100% for patients treated with RALP and 80-97% for patients treated with RRP [326]. A similar study reported mean potency recovery rates at 12 months of 55-81% for patients treated with RALP and 26-63% for patients treated with RRP [325]. The major limitations of the included studies were the frequent retrospective study design and the use of different assessment tools preventing a proper comparison between techniques and series. In a prospective, controlled, non-randomised trial RALP performed modestly better in preserving erectile function compared with open RP, without a statistically significant difference for urinary incontinence or surgical margins [314]. RALP and open RP have comparable functional outcomes and similar HRQoL scores [630].

There are no reliable data to compare HRQoL following RALP and laparoscopic RP. In a controlled cohort study comparing HRQoL after open and laparoscopic RP urinary bother was worse in the laparoscopic RP group at one and three months, but did not differ between the groups thereafter. Bowel and sexual function and bother were similar in the two groups [631].

Age and baseline scores are significant factors impacting functional outcome and HRQoL after RP. Older age has a significant adverse effect on recovery of continence and potency [632]. Younger men reported higher initial sexual and urinary function overall, and experienced greater decreases in sexual function immediately after RP and at 1 year than older men, with similar decrease rates in urinary function and bother. Relative sexual function decreases at 2 years were similar [633]. The same study showed that declines in quality domains are higher in men with above average baseline scores regardless of age.

General HRQoL domains such as pain and energy worsen immediately post-RP, but usually improve by 12 months [629].

New methods for reporting outcomes after RP combine major outcomes, including continence, potency and cancer control [310] and peri-operative complications and positive surgical margins [634]. Pentafecta rates reflect post-operative expectations and satisfaction more accurately and are used in counselling patients with clinically localised PCa. The use of trifecta and pentafecta outcomes in post-operative HRQoL assessment needs further validation.

6.8.4 *External-beam radiotherapy and low-dose rate brachytherapy*
External-beam radiotherapy and I-125 LDR brachytherapy is associated with acute and late GU or gastrointestinal toxicity with impact on erectile function. In contemporary practice, the NCIC toxicity grading system is increasingly used, but most studies have used the RTOG scales, which are described in Tables 6.8.1 and 6.8.2. Risk factors for acute or late gastrointestinal toxicities after RT include advanced age, pre-existing diabetes mellitus, haemorrhoids, inflammatory bowel disease, a history of prior abdominal surgery, larger rectal volume and the concomitant use of androgen deprivation [469].

Pre-treatment GU complaints, prior TURP and the presence of acute GU toxicity are suggested as contributing to long-term urinary morbidity.

Table 6.8.1: 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.* [635]*.

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 (*day: 12-16 times; nocturia 5-8 times*). Dysuria, urgency, bladder spasm requiring local anaesthetic.	Frequency of urination is more frequent than every hour (*day: >16 times; nocturia: > 8 times*). Dysuria, bladder spasm, urgency requiring frequent regular narcotic. Gross haematuria *complaints requiring permanent or suprapubic catheter*.	Haematuria requiring transfusion Obstruction not resulting from Clots. Ulceration Necrosis

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GI = gastrointestinal; GU = genito-urinary.

Table 6.8.2: 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.* [635]*

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	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	Frequency during day: 1-2 h Nocturia 4-6/night Moderate dysuria or intermittent (mild, moderate) haematuria requiring medication[†] Moderate telangiectasia Bladder capacity: 150-300 mL	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	Necrosis Severe haemorrhagic cystitis Bladder capacity >100 mL
* 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.				

*Reproduced with permission of Elsevier, from Budäus L et al. Eur Urol 2012 Jan;61(2):112-7.
GI = gastrointestinal; GU = genito-urinary; TURP = transurethral resection of the prostate.

In a large prospective longitudinal study assessing HRQoL and satisfaction with outcome in PCa survivors the effects of EBRT on urinary symptoms had resolved at 12 months and improved over baseline at 24 months [625]. Patients in the LDR brachytherapy group reported significant detriments in urinary irritation or obstruction and incontinence. At 1-2 years after LDR brachytherapy, incontinence was reported by 4-6% of patients. Eighteen percent of the LDR brachytherapy group and 11% of the EBRT group reported distress from overall urinary symptoms at 1 year [625].

External beam radiotherapy and LDR brachytherapy significantly affect the bowel and rectal HRQoL domains [625], which are almost as important as urinary problems [636, 637]. Symptom onset occurs during or early after treatment, and sometimes persists into follow-up. Rectal urgency, frequency, pain, faecal incontinence, or haematochezia-caused distress related to bowel function was reported in 9% of patients at 1 year after EBRT or LDR brachytherapy [625]. At 2 years after dose-escalated EBRT, ≤ 11% of patients had problems with bowel HRQoL. Bowel HRQoL was related to baseline function, ≤ 25% volume of rectum treated with 70 Gy, and aspirin [638]. Bowel and rectal symptoms were less severe after LDR brachytherapy than EBRT [615].

Overall, the HRQoL at 6 years after LDR brachytherapy did not significantly differ from baseline. Changes in symptoms scores returned to approximately baseline values at 1 year and remained stable up to 6 years after treatment. The only clinically relevant changes occurred in sexual activity. At 6 years after treatment, 70% of the patients had diminished sexual activity compared with baseline, 12% had improved sexual activity, and 18% had no change in sexual activity [639].

Contemporary RT techniques, like IMRT with IGRT is associated with lower rates of severe toxicity and a high HRQoL [640]. At 4 years, freedom from grade 2 GI and GU toxicity was 92% and 76%, respectively. Bowel domain remained stable over the 2-year follow-up period and was higher for patients who met ideal rectal constraints [641].

Dietary intervention did not significantly affect gastrointestinal side effects or other aspects of HRQoL in patients undergoing RT [642].

Among general domains fatigue is most commonly reported following EBRT, with the highest level seen at the end of treatment. Four percent of patients reported severe fatigue 5-years post-treatment, adversely affecting HRQoL [643]. Men treated with interstitial LDR brachytherapy had only slight declines in general HRQoL. Physical and functional status declines have been reported in the first few months after implantation, but pre-treatment function was regained by most men after 1 year [639].

Adjuvant ADT may exacerbate the adverse effects of EBRT or LDR on sexuality, vitality [625] and long-term bowel function [644]. 18 months of adjuvant ADT led to earlier testosterone recovery and better QoL compared to 36 months of adjuvant ADT [645].

6.8.5 Complications of high-intensity focused ultrasound
Urinary retention appears to be one of the most common side-effects of HIFU, developing in almost all

patients, with the mean interval of catheterisation via a suprapubic tube varying between 12 and 35 days [503, 646, 647]. Grade I and II urinary stress incontinence occurs in about 12% of patients. Subsequent TURP or bladder neck incision to treat subvesical obstruction is common, and is sometimes even performed at the time of HIFU. Post-operative impotence occurs in 55-70% of patients.

Elterman *et al.* [648] have treated 95 patients with clinically organ-confined PCa using the Sonablate 500 device (SonaCare Medical, Charlotte, NC, USA) and have evaluated the type and frequency of treatment-associated complications. With a minimum follow-up of six months, 17% (7/41) of the men had significant incontinence, and 2% developed significant ED. Early and late subvesical obstruction necessitating surgical treatment occurred in 17 (17.9%) and 20 (21.1%) patients, respectively.

Moderate to severe stress urinary incontinence was rare, occurring in fewer than 6.4% of men, and decreased in more recent treatment to 3.1% [649]. Acute urinary retention was seen in 7.6% of men. Even in more recent treatment, the rate of urethral-rectal fistula was 0.7%.

Health-related QoL outcomes following primary HIFU therapy have not been prospectively studied using validated questionnaires. High complication rate after HIFU treatment is presumably associated with a clinically significant reduction in the urinary and sexual function domains and requires further investigation.

6.8.6 *Cryotherapy*

6.8.6.1 *Complications of cryosurgery for primary treatment of PCa*

Erectile dysfunction occurs in about 80% of patients and this remains a consistent complication of the CSAP procedure, independent of the generation of the system used [650]. The complication rates described in third-generation cryosurgery include tissue sloughing in about 3%, incontinence in 4.4%, pelvic pain in 1.4% and urinary retention in about 2% [651-656]. The development of fistula is usually rare, being < 0.2% in modern series. About 5% of all patients require TURP for subvesical obstruction.

Quality of life and sexual function following CSAP were investigated in a clinical phase II trial that recruited 75 men [657]. Quality of life analysis with the prostate-specific FACT-P questionnaire showed that most subscales return to pre-treatment levels by 12 months after CSAP. Furthermore, no significant changes were seen when comparing data at 36 months with those at 12 months. With regard to sexual function, 37% of men were able to have intercourse three years after CSAP.

In a prospective, randomised clinical trial, 244 men with newly diagnosed organ-confined PCa were randomised to receive either EBRT or to undergo CSAP [658]. After three year of follow up, sexual function was significantly less impaired in the EBRT group.

6.8.7 *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 6 months, with more frequent diarrhoea and worse emotional functioning, compared with castration alone [659]. 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 [660]. A prospective observational study of non-metastatic PCa, found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [661]. 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 [662].

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 12 months [663]. 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 [664], preserved libido and erectile function [665].

Intermittent androgen deprivation has been discussed elsewhere (see Section 6.6 - Metastatic PCa - Hormonal therapy).

6.8.7.1 *Side-effects, quality of life and cost of hormonal therapy*

The many deleterious side-effects of long-term ADT have been well known for years. As the use of ADT increases, it is increasingly important to consider these side-effects. A systematic review of the side-effects of long-term ADT has recently been published [666].

6.8.7.1.1   Sexual function
Loss of libido and ED are common. The management of acquired ED is mostly non-specific [667].

6.8.7.1.2   Hot flushes
Hot flushes are the most common side-effect of ADT. They appear 3 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. Soya 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 [668].

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 [669]. After 6 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 [670], the efficacy of clonidine, veralipride, gabapentine [671] and acupuncture [672] must be compared in prospective, randomised, controlled trials.

6.8.7.1.3   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.

6.8.7.1.3.1 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) [673]. Hip fractures in men are associated with a significant risk of death [674]. 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 [675]. Both changes increase the fracture risk.

•   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.

•   Hormonal treatment modalities
Bicalutamide monotherapy could be a bone-protective treatment [676, 677], 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 [562].

•   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 [678] or yearly [679] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [680]. A quarterly regimen could be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [681].

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 8 years of follow-up [682]. This benefit has never been observed with more recent bisphosphonates.

•   Denosumab (a fully human monoclonal antibody against receptor activator of NF-kappaB 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 2 years, using a 60 mg subcutaneous regimen every 6 months [683]. 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 4 weeks), a delay in bone metastases of 4.2 months has been shown [684] without any impact on OS, but with an increase in side effects. Therefore, this regimen cannot be recommended.

6.8.7.1.3.2 Metabolic effects
Lipid alterations are common and may occur as early as the first 3 months of treatment [675]. 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 [685], 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 [686]:
• waist circumference > 10^2 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 [687].

6.8.7.1.3.3 Cardiovascular morbidity
Cardiovascular mortality is now the most common cause of death in PCa patients, even exceeding PCa mortality [688]. Several studies showed that ADT, after only six months, was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [689]. The RTOG 92-02 [690] and 94-08 [398] 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 [691]. 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 [692] or presenting with a metabolic syndrome [693].

It has been suggested that LHRH antagonists might be associated with less cardiovascular morbidity compared to agonists [694]. 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 [695]. Preventive advice includes non-specific measures: loss of weight, increased exercise, improved nutrition and smoking cessation.

6.8.7.1.3.4 Fatigue
Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure [696, 697], with prolonged efficacy [698] and improved specific survival [699].
        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 [666].

6.8.8   Comparison of health-related quality of life between treatment modalities
So far, most comparisons between treatment-related QoL were assessed in non-randomised observational cohorts, with limited follow-up. Only a few trials have directly compared treatment modalities. When comparing general HRQoL for treatments of clinically localised PCa [614, 700] the differences were limited. Data from longitudinal studies show that surgery and RT have a greater impact on role functioning and vitality/energy with surgery being associated with increased dysfunction [701]. Most men recovered function by one year post treatment.

Disease-specific outcomes of PCa, including urinary, bowel and sexual functioning, differ between treatment modalities, with the magnitude of adverse impact of treatment being time-depended. Urinary incontinence

increased sharply after RP, whereas bowel problems and urinary irritation-obstruction occur after EBRT and LDR brachytherapy [615]. Sexual function deteriorates immediately after surgery and then improves, whereas sexual function continued to slowly decline after EBRT and brachytherapy. At one year RP incurred a significantly higher incidence of urinary incontinence (39-49%) and ED (80-91%) compared with RT (6-7% and 41-55%, respectively) [636]. Bowel problems (urgency) affected 30-35% of the EBRT group vs. 6-7% of the RP group [636].There was no change in urinary function after surgery and little change in bowel function after ERBT after 1 year [615]. Patients with bowel dysfunction at one year after EBRT treatment may expect only modest improvement. Although diarrhoea continues to subside, there is little change in tenesmus and rectal urgency, while rectal bleeding becomes more prevalent. Patients treated with LDR brachytherapy had significantly higher urinary function scores at 0-6 months after treatment (84.5%) than patients treated with RP (63.3%) [702]. Urinary bother did not differ significantly (67.7% vs. 67.4%, respectively). Decreased sexual function did not return to pre-treatment levels in either group.

Short-term (up to 2 years) outcomes of open RP, RALP, brachytherapy, and cryotherapy were compared in a non-randomised cohort of patients [703]. At a mean follow up of 24 months LDR brachytherapy and prostate cryoablation were associated with better urinary function and bother scores compared to open RP and RALP. Brachytherapy and cryotherapy had a 3-fold higher rate of return to baseline urinary function compared to open RP and RALP. Sexual function and bother scores were highest after brachytherapy, with a 5-fold higher rate of return to baseline function compared to cryotherapy, open RP and RALP. All 4 treatments were associated with relatively transient and less pronounced impact on bowel function and bother [703].

Longer (3 years) follow-up confirmed time-dependent changes in adverse effects, e.g., increased urinary symptoms after EBRT or increased sexual dysfunction after LDR brachytherapy, which tended to reduce any differences between treatments over time [704]. RP caused greater deterioration in urinary incontinence and sexual function, but improved urinary irritative-obstructive symptoms compared with LDR brachytherapy. Treatment differences persisted for up to 3 years [704].

At 5 years, incontinence was reported in 14-16% of RP and 4% of EBRT patients. Bowel urgency and painful haemorrhoids were more common in the EBRT group. Sexual function declined similarly in both groups. Erectile dysfunction was more prevalent in the RP group (79.3 vs. 63.5%) [628].

A randomised comparative trial of RP and LDR brachytherapy was closed after 2 years due to poor accrual [705]. After median follow up of 5.2 years for LDR brachytherapy vs. RP, there were no differences in bowel or hormonal domains. LDR brachytherapy patients scored better for urinary QoL and sexual domains, and patient satisfaction.

At 15-year follow up, there were no significant differences in disease-specific functional outcomes between RP and EBRT, which were seen at 2 and 5 years follow up in the PCOS study [706].

In a population-based study of PCa survivors, up to 18 years post-diagnosis, men treated with RP had clinically worse urinary bother and sexual functioning; those treated with EBRT with/without concurrent ADT had the worst bowel symptoms, sexual activity, fatigue, pain and dyspnoea. Despite this, there was no statistically or clinically significant difference in global HRQoL between men treated with RP, EBRT with concurrent ADT or observation, which may be explained by change in perception of symptoms by PCa survivors ('response shift'), when survival is prioritised above symptoms experienced or physical limitations [707]. In the same study men treated with brachytherapy had the highest global HRQoL and men treated with ADT alone the lowest. However, the somewhat overly positive outcome of brachytherapy should be interpreted with caution, because of selection bias, and under-estimation of irritative voiding symptoms by the EORTC questionnaire.

A study in Norway investigated the relationship between urinary, bowel or sexual dysfunction and global HRQoL in PCa survivors, including untreated patients [624]. Irritative-obstructive urinary symptoms and poor sexual drive were independently associated with low global HRQoL, whereas erectile function and use of medication for ED were not [624]. All typical adverse events (moderate/severe IPSS, urinary incontinence, irritative intestinal symptoms, faecal leakage, poor sexual drive and poor erectile function) were significantly associated with low global HRQoL in univariate analyses. Low educational level, comorbidity and moderate or high neuroticism were all significantly associated with low global HRQoL in univariate analyses. No significant associations with global QoL were observed for age, a paired relationship or D'Amico risk group.

Many men treated for clinically localised PCa experience post-treatment problems that may affect their daily lives. Each patient must decide which side-effect profile is most acceptable when making treatment decisions.

Recommendation	LE	GR
Inform patients with low-risk PCa that the functional outcomes of active surveillance are better than for local active treatment.	2	B
Inform patients that functional outcomes after RALP and open prostatectomy are similar.	2	B
Inform Patients that long-term (15 years) QoL outcomes of EBRT and RP are similar.	2	B

EBRT = external beam radiation therapy; RALP = robot assisted laparoscopic prostatectomy; RP = radical prostatectomy; QoL = quality of life.

6.9 Summary of guidelines for the primary treatment of prostate cancer

EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Low-risk	**Intermediate-risk**	**High-risk**	
Definition	PSA < 10 ng/mL and GS < 7 and cT1-2a	PSA 10-20 ng/mL or GS 7 or cT2b	PSA > 20 ng/mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			Locally advanced

Primary treatment of prostate cancer			GR
General comments	Discuss several treatment modalities (active surveillance, surgery and radiotherapy) with patients suitable for such treatments.		A*
	In patients who are surgical candidates for radical prostatectomy, 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 EBRT to all risk groups of non-metastatic PCa.		A
	Offer IMRT for definitive treatment of PCa by EBRT.		A
	Treatment	**Comment**	
Low risk PCa	**Watchful waiting**	Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.	A
		While on watchful waiting, base the decision to start non-curative treatment on symptoms and disease progression.	B
	Active surveillance	Offer active surveillance to patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	A
		Base follow-up on DRE, PSA and repeat biopsies. The optimal follow-up interval is still unclear.	A
	Radical prostatectomy	Offer RP to patients with a life expectancy > 10 years.	A
		Offer a nerve-sparing surgery in pre-operatively potent patients with low risk of extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/ nomograms).	B
		Do not perform LND in low-risk PCa	A
	Radiotherapy	In low-risk PCa, the total dose should be 74 to 78 Gy.	A
		In patients with low-risk PCa, without a previous TURP and with a good IPSS and a prostate volume < 50 mL, offer LDR brachytherapy.	A
	Cryotherapy, HIFU	Only offer cryotherapy and HIFU within a clinical trial setting. The lack of long-term efficacy compared to standard modality has to be discussed with patients.	C

	Focal treatment	Do not offer focal therapy of PCa as a therapeutic alternative outside clinical trials.	A
	Androgen suppression	Unsuitable.	A
Intermediate risk PCa	**Watchful waiting**	Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.	A
	Active surveillance	Not an option.	A
	Radical prostatectomy	Offer RP to patients with a life expectancy > 10 years.	A
		Offer a nerve-sparing surgery in pre-operatively potent patients with low risk of extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	B
		In intermediate- risk, extracapsular disease, use mpMRI as a decision tool to select patients for nerve-sparing procedures.	B
		Perform an eLND if the estimated risk for positive lymph nodes 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 HT for pN0.	
	Radiotherapy	In intermediate- risk PCa use a total dose of 76-78 Gy, in combination with short-term ADT (4-6 mo).	A
	Androgen suppression monotherapy	No place in asymptomatic patients.	A
High risk PCa	**Watchful waiting**	High risk localised: Offer watchful waiting to patients not eligible for local curative treatment and those with a short life expectancy.	
		High risk locally advanced: In locally advanced M0 patients unwilling or unable to receive any form of local treatment, offer a deferred treatment policy using ADT as monotherapy 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 NHT before RP.	A
		Perform an eLND in high-risk PCa.	A
		Do not perform a limited LND.	A
		High risk localised: Offer RP in a multimodality setting to patients with high-risk localised PCa and a life expectancy of > 10 years.	B
		Offer nerve-sparing surgery in pre-operatively potent patients with low risk of extracapsular disease (refer to Partin tables/nomograms).	B
		In high-risk disease, use multiparametric MRI as a decision-making tool to select patients for nerve-sparing procedures.	B
		High risk locally advanced: Offer RP in a multimodality setting to highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1). Do not consider nerve sparing surgery.	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	In patients with high-risk localised PCa, use a total dose of 76-78 Gy in combination with long-term ADT (2-3 years is recommended).	A
		In patients with locally advanced cN0 PCa, offer radiotherapy in combination with long-term ADT (2-3 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
N1 patients			
cN1	In patients with cN+ PCa, offer pelvic external beam irradiation in combination with immediate long-term ADT.		B
pN1 after eLND	Offer adjuvant ADT for node-positive (pN+).		A
	Offer adjuvant ADT with additional radiotherapy.		B
	Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes showing microscopic involvement, with a PSA < 0.1 ng/mL and absence of extranodal extension.		B
Metastatic PCa	**Watchful waiting**	In M1 asymptomatic patients, deferred castration should be discussed with a well-informed patient.	B
	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 (LHRH agonist or antagonist).	A
		Offer castration combined with chemotherapy to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.	A
		Offer castration alone with or without an antiandrogen to patients unfit for, or unwilling to consider castration combined with chemotherapy.	A
		Do not offer castration combined with local treatment/ other new hormonal treatments (abiraterone acetate or enzalutamide) outside clinical trials.	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 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 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 7 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 6-7 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
		In M1 patients, offer combined treatment with LHRH agonists and NSAA when an intermittent modality is used.	A
Castrate resistant status	Ensure that testosterone levels are confirmed as < 50 ng/mL, before diagnosing mCRPC.		A
	Do not treat patients for <u>non-metastatic</u> CRPC outside of a clinical trial.		A
	Counsel, manage and treat patients with mCRPC in a multidisciplinary team.		A
	In men treated with maximal androgen blockade, stop anti-androgen therapy once PSA progression is documented. *Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.*		A
	Treat patients with mCRPC with life prolonging agents. Base the choice of first line treatment on the performance status, symptoms, comorbidities and extent of disease (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).		A
	Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m^2 every 3 weeks.		A
	In patients with mCRPC and progression following docetaxel chemotherapy, offer further life-prolonging treatment options, which include cabazitaxel, abiraterone, enzalutamide and radium-223.		A
	Offer bone protective agents to patients with skeletal metastases to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis, in particular, must be avoided.		A
	Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.		A
	Treat painful bone metastases early on with palliative measures such as external beam radiotherapy, radionuclides, and adequate use of analgesics.		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.		A

*Upgraded following panel consensus.

ADT = androgen deprivation therapy; DRE = digital rectal examination; EBRT = external beam radiation therapy; HIFU = high-intensity focused ultrasound; HT = hormonal therapy; IPSS = International Prostate Symptom Score; LDR = low-dose-rate; LHRH = luteinising-hormone-releasing hormone; eLND = (extended) lymph node dissection; IMRT = intensity-modulated radiotherapy; LN = lymph node; mCRPC = metastatic castrate-resistant prostate cancer; mpMRI = multiparametric magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; NSAA = non-steroidal anti-androgen; PSA-DT = PSA doubling time; RP = radical prostatectomy; TURP = transurethral resection of the prostate.

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 vulnerable patients (reversible impairment) after resolution of geriatric problems; 3. Offer adapted treatment to frail patients (irreversible impairment). 4. Offer only symptomatic palliative treatment to patients who are too sick with terminal illness.	B

Recommendations for management	LE	GR
Localised disease		
Offer standard t reatment to fit and vulnerable 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 frail or 'too-sick' senior adults, offer immediate ADT only for symptom palliation.	1b	A
Offer minimally invasive energy-ablative therapies only to selected fit and vulnerable 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 vulnerable adults.	1b	B

ADT = androgen deprivation therapy; PSA = prostate specific antigen; TRUS = transrectal ultrasound;

6.10 Treatment of PSA-only recurrence after treatment with curative intent

6.10.1 Background

Primary curative procedures such as RP and RT are well-established therapeutic options in the management of localised PCa. Despite technical improvements, there is still a significant risk of cancer recurrence after therapy. Between 27% and 53% of all patients undergoing RP or RT develop PSA-recurrence (see Sections 6.2 and 6.3). While a rising PSA level universally precedes metastatic progression and PCSM, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a PSA rise is not a surrogate for these survival endpoints. 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 has to be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

6.10.2 Definitions

6.10.2.1 Definition of biochemical failure

The PSA level that defines treatment failure differs between men who have undergone RP and those who have received RT. However, following RP, there is international consensus that recurrent cancer may be defined by two consecutive PSA values of > 0.2 ng/mL and rising [708]. A retrospective analysis including 2,782 men who had undergone RP for clinically localised PCa [709] was used to determine the best PSA cut-off point for defining BCR. Once PSA recurrence was detected, there was a subsequent increase in PSA in 49%, 62%, and 72% of patients with PSA levels of 0.2, 0.3, and 0.4 ng/mL, respectively [709].

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 [710].

Importantly, patients with PSA-recurrence after RP or primary RT have different risks of subsequent PCSM. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments.

6.10.3 Natural history of biochemical failure

Once a PSA relapse has been diagnosed, it is important to determine 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 doubling time [PSA-DT] and interval to PSA failure).

6.10.3.1 Post-radical prostatectomy biochemical failure

According to Pound *et al.* [375], not all patients with BCF after RP develop clinical recurrence. The authors evaluated the follow-up data for 1,997 patients after RP, and only 34% of those with BCF subsequently had a clinical recurrence. These data were confirmed by Boorjian *et al.* in a study including approximately 2,400 patients; only a minority of those with BCF after RP developed a clinically evident recurrence (22.9%) and only a few died of PCa (5.8%) [711]. Overall, these studies demonstrated a general trend among men with PSA-only recurrence after RP (i.e. 7-40% of relapsing men): for every 100 men treated with RP, approximately 15-30 will develop BCR and 2-6 of those will die of PCa.

Several studies have attempted to identify risk factors for metastases and PCSM in patients experiencing PSA-only recurrence following RP. Compiling the results of several studies, a subgroup with a high risk of metastases and PCSM was characterised by a PSA-DT < 3 months, SVI (pT3b), specimen Gleason score 8-10, or time to PSA-recurrence < 3 years. Furthermore, a low-risk subgroup was defined as patients with a PSA-recurrence > 3 years following surgery, specimen Gleason score < 7, pathologic organ-confined disease and limited extracapsular extension (pT3a), and PSA-DT > 12 months [712-715]. Patients in the high-risk subgroup universally have an exponentially higher risk of developing metastases and dying of PCa.

Patients in the low-risk subgroup typically respond very well to salvage RT with a high probability of PSA being undetectable [716]. 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 [717]. Trock *et al.* demonstrated that salvage RT was associated with a significant 3-fold increase in PCa-specific survival relative to those who received no salvage treatment. The increase in PCa-specific survival associated with salvage RT 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 [717].

6.10.3.2 Post-radiotherapy biochemical recurrence

Similar to patients experiencing PSA-recurrence after RP, patients with a PSA-rise following RT can be subdivided into prognostic categories. A high-risk subgroup with elevated risk of metastases and PCSM are those patients with a PSA-DT < 3 months, time to biochemical progression < 3 years, biopsy Gleason score 8-10 or clinical stage cT3b-T4. Conversely, patients at low risk of metastases and PCSM are those with a PSA-DT > 15 months, biopsy Gleason score < 7, clinical stage < cT3a and time to biochemical progression > 3 years [714, 718, 719].

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 biochemical progression < 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 factors [719].

6.10.4 *Assessment of metastases*
6.10.4.1 Bone scan and abdominopelvic computed tomography

The standard workup to detect PCa metastases usually includes a bone scan and abdominopelvic CT. However, because BCF after RP or RT precedes clinical metastases by 7-8 years on average, the diagnostic yield of common imaging techniques is poor in asymptomatic patients [720]. In men with PSA-only relapse after RP, the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [721, 722].

Only 11-14% of patients with BCF after RP have positive CT [721]. In a series of 132 men with BCF after RP, the mean PSA level and PSA velocity associated with positive CT was 27.4 ng/mL and 1.8 ng/mL/ month, respectively [723]. Therefore, bone scan and abdominopelvic CT should only be considered in patients with BCF 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 [721, 723].

6.10.4.2 Choline and Acetate positron emission tomography (PET)/computed tomography (CT)

In patients with BCF, choline or acetate PET/CT has reported sensitivities and specificities of 55-96% and 57-100%, respectively [241, 724-726]. Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [727] and may be positive for bone metastases in up to 15% of patients with BCF after RP and negative bone scan [728]. The specificity of choline PET/CT is also higher than bone scan with less false positive and indeterminate findings [249, 729]. Detection of lymph node 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 [241, 724, 726, 730]. In patients

with BCF 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 recent 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 [724].

Despite these limitations, choline PET/CT may change medical management in 18-48% of patients with BCF after primary treatment [731-734]. Positron emission tomography/computed tomography can detect metastases missed by conventional imaging thereby prompting palliative management rather than useless and potentially morbid salvage treatments. It can also trigger aggressive metastasis-directed therapy in oligometastatic patients [735]. Conversely, a PET/CT examination showing only local relapse may lead to salvage therapy in patients initially scheduled for palliative treatment. 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) [734].

Positron emission tomography/computed tomography cannot be recommended in all patients, but should be limited to patients who are fit enough for curative salvage treatment.

After RP, the optimal PSA cut-off level for PET/CT analysis seems to be between 1 and 2 ng/mL [726, 730]. It is unclear whether PSA velocity or PSA-DT thresholds can be used to further select groups of patients in whom PET/CT could be recommended.

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 [726]. 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 [736]. In another study of 140 patients the choline PET/CT detection rate was not influenced by the PSA level, but only by PSA kinetics [737].

6.10.4.3   Other radionuclide techniques
A [111]In-capromab pendetide scan (ProstaScint™) yielded disappointing results in patients with BCF after RP or RT [720, 721]. Its use is therefore not recommended. [68]Ga-PSMA PET is considered still experimental in this setting. [18]F-Fluoride PET and PET/CT have a higher sensitivity than bone scan in detecting bone metastases [729]. However, [18]F-Fluoride is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [249].

6.10.4.4   Whole-body and axial magnetic resonance imaging (MRI)
Little is known regarding the accuracy of whole-body or axial MRI in patients with BCF after RP or RT [738]. Therefore, the role of these techniques in detecting occult bone or lymph node metastases in the case of BCF remains to be assessed.

6.10.4.5   Assessment of local recurrences
6.10.4.5.1 Local recurrence after radical prostatectomy
The precise localisation of the local recurrence by imaging techniques is needed only if histological proof of the recurrence is mandatory before salvage treatment and/or if this 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 [720]. As a consequence, salvage RT is usually decided on the basis of the BCF, 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 salvage RT without local imaging.

Nonetheless, 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 84-88% and 89-100%, respectively [739-741]. However, the mean PSA level in these studies was 0.8-1.9 ng/mL, which is higher than the 0.5 ng/mL threshold usually used for salvage therapy. Recently, two studies evaluated mpMRI in patients with PSA level < 0.5 ng/mL. One found a sensitivity of only 13% in men with PSA level < 0.3 ng/mL [742], while the other reported a sensitivity of 86% in patients with PSA level < 0.4 ng/mL [743]. Therefore, it remains to be seen whether MRI is able to correctly detect local recurrences in patients with PSA level < 0.5 ng/mL in order to allow a stereotaxic boost to the recurrence site during salvage RT. Choline or acetate PET/CT can also detect local recurrences, but are less sensitive than MRI [725, 744].

6.10.4.5.2 Local recurrence after radiation therapy
In patients with BCF 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 necessary to obtain histological proof of the local recurrence before treating the patient [720].

Transrectal US is not reliable in depicting local recurrences after RT. In contrast, mpMRI has yielded excellent results [720, 745-748] and can be used for biopsy targeting and guiding local salvage treatment. Detection of recurrent cancer is also feasible with choline and acetate PET/CT, but PET/CT has poorer spatial resolution than MRI [731, 732, 737, 749].

6.10.4.6   Guidelines for imaging in patients with biochemical failure

PSA recurrence after RP	LE	GR
PSA < 1 ng/mL: no imaging is recommended.	3	A
PSA ≥ 1 ng/mL: choline PET/CT imaging is recommended.	2b	A
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
PSA recurrence after RT		
Perform prostate 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

CT = computed tomography; mpMRI = mutiparametric magnetic resonance imaging; PET = positon emission tomography; PSA-DT = prostate-specific antigen doubling time.

*6.10.5   **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 (CAD, AD);
- Intermittent androgen deprivation (IAD);
- Observation.

Following RT, the same therapeutic options - with the exception of repeat percutaneous RT - may apply in relation to PSA recurrences. In addition, salvage RP, cryotherapy or brachytherapy may be indicated in carefully selected patients.

6.10.5.1   Radiotherapy (Salvage radiotherapy [SRT] - 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 [495, 750-752], providing patients with a ~80% chance of being progression-free 5 years later [496].
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 salvage RT alone (n = 160) within 2 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 [717]. Despite the indication for salvage RT, a "wait and see" strategy is an option in patients with a long PSA-DT of > 12 months [711]. For an overview see Table 6.10.1.

Table 6.10.1: Selected studies on post-prostatectomy salvage radiotherapy (SRT), sorted by pre-salvage radiotherapy (SRT) PSA level*

Reference	Year	n	HT %	pre-SRT PSA (ng/mL) median	Median dose (Gy)	bNED / PFS year	5-yr results
Siegmann, *et al.* [753]	2011	301	0	0.28	66.6 / 70.2	74% (2)	55% vs.88% @ 66.6 vs. 70.2 Gy
Wiegel, *et al.* [496]	2009	162	0	0.33	66.6	54% (3.5)	60% vs. 33% @ PSA ≤ 0.5 vs. > 0.5
Goenka, *et al.* [754]	2011	285	31	0.4	> 70 (72%)	37% (7)	39%
Cremers, *et al.* [755]	2010	197	0	0.59	63 /2.25 frct. (88%)	59% (5)	
Bernard, *et al.* [756]	2010	364	0	0.6	64.8	50% (5)	
Buskirk, *et al.* [757]	2006	368	15	0.7	64.8	46% (5)	63% vs. 51% @ PSA < 0.5 vs. 0.5-1.0
Pazona, *et al.* [758]	2005	223	4.5	0.8	63	40/25% (5/10)	42% vs. 30% @ < 1.3 vs. ≥ 1.3
Pisansky, *et al.* [759]	2000	166	4	0.9	64	46% (5)	61% vs. 36% @ PSA ≤ 1 vs. > 1
Soto, *et al.* [760]	2012	441	24	< 1 (58%)	68	63/55% (3) HT / no HT	44/40% HT / no HT
Stephenson, *et al.* [495]	2007	1540	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.

The addition of HT to salvage RT (n = 78) was not associated with an additional increase in the CSS compared with salvage RT alone [717]. So far, adding ADT to salvage RT has only shown benefit in terms of biochemical PFS after 5 years in retrospective series [754, 761] and in PFS for "high-risk" tumours [760], however data from prospective randomised trials are lacking. Results are awaited from recently completed randomised controlled phase III studies: the Radiation Therapy Oncology Group RTOG 96-01 comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the post-operative setting and the French GETUG 16 trial, comparing salvage EBRT with- or without 6 months of ADT. To date there is no recommendation for patients with primary pN0- stage at RP for a combination of salvage RT plus additional ADT.

6.10.5.1.1 Dose, target volume, toxicity
The optimal salvage RT 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 according to the pathological stage after RP) [750]. Similarly, a USA guideline panel regarded 64-65 Gy as the minimum dose that should be delivered post RP [762]. However, more recent data suggest that higher total doses can achieve higher rates of biochemical control at 3-5 years [756]. In a systematic review, the pre-salvage RT PSA level and salvage RT 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 [750, 763, 764].

There have been various attempts to define common outlines for "clinical target volumes" of PCa [765-767] and for organs at risk of normal tissue complications [768]. However, depending on the applied techniques and accepted constraints, a satisfactory consensus has not yet been achieved.
In one report on salvage RT with 66.6-70.2 Gy in 1.8 Gy fractions, only 2.7% of the patients had moderate proctitis or cystitis grade II. Four patients (1.3%) had grade III cystitis. Six out of 301 patients (2%) developed urethral stricture which was not solely attributable to salvage RT but also resulted from RP alone [751]. In a retrospective cohort of 285 men receiving 3D-CRT (38%) or IMRT (62%) with 66 Gy in 95% of cases, the high-dose subgroup did not show a significant increase in toxicity [754]. In an analysis involving 30 participating centres, a quality assurance programme assessing target volumes, RT techniques (3D-CRT, IMRT,

VMAT) and RT doses (64 vs. 70 Gy) it was found that 3D-CRT was applied in nearly half of the centres and was not associated with significantly worse rectum and bladder dose-volume histogram parameters, for salvage RT using 70 Gy, when compared with IMRT [769].

However, with dose escalation (72 Gy) or up to a median of 76 Gy, the rate of severe side effects especially for the genito-urinary system clearly increases, even with newer planning and treatment techniques [770, 771]. 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 (5-yr: 3D-CRT 15.8% vs. IMRT 16.8%) [770]. After a median salvage IMRT dose of 76 Gy, the 5-year risk of grade 2-3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [771].

6.10.5.1.2 Comparison of adjuvant radiotherapy (ART) and salvage radiotherapy (SRT)
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 salvage RT does not impair PCa control, but clearly helps to reduce overtreatment which is a major issue in ART [772].

Both approaches (ART and SRT) together with the efficacy of neoadjuvant HT are currently being compared in three prospectively randomised clinical trials: 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. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of RT when it is used, and provides justification when it is not, this will help the discussion between the physician and the patient.

6.10.5.2 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 systematic review using studies published from 2000 onwards [4]. 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 early HT group) [773]. Other studies did not find any differences between early versus delayed, or no, HT. One study found an unfavourable effect of HT [774]. 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 [711], 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 [717]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [775]. 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.

The link between PSA relapse and survival is weak at best, and the management approach has to be individualised [717, 719]. 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 [695, 776]. However, high-risk patients with a long life expectancy may benefit from HT. Therefore, personalised risk stratification is warranted, taking patient-specific (age, comorbidity, patient preferences) and disease-specific (Gleason score, PSA-DT) factors into account in clinical decision-making.

Based on currently available evidence, the benefit of early systemic HT for non-metastatic PCa relapse remains unproven. Accordingly, early HT cannot be systematically recommended in the setting of biochemical or local disease recurrence. 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.

6.10.5.3   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 these patients, the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years [375].

6.10.6   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 [777-786]. As a general rule, 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.

6.10.6.1   Salvage radical prostatectomy (SRP)
Salvage RP 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.

6.10.6.1.1 Oncological outcomes
In a recent systematic review of the literature, Chade *et al.* showed that SRP gave 5- and 10-year biochemical recurrence-free survival (BCR-FS) estimates ranging from 47-82% and from 28-53%, respectively. The 10-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 [787].

      In most contemporary series, organ-confined disease, negative surgical margins (SM), and the absence of seminal vesicle and/or lymph node metastases were favourable prognostic indicators associated with a better disease-free survival of approximately 70-80%, in comparison with 40-60% in patients with locally advanced PCa [786].

Table 6.10.2: Oncological results of selected SRP case series, including at least 30 patients

Reference	Year	n	Median FU (mo)	Pathologic organ confined, %	PSM, %	Lymph node involve- ment, %	BCR-free probability, %	CSS, %	Time probability, yr
Sanderson, et al. [788]	2006	51	-	25	36	28	47	-	5
Leonardo, et al. [789]	2009	32	35	53	34	0	75	-	3
Heidenreich, et al. [785]	2010	55	23 (2-56)	73	11	20	87	-	2
Chade, et al. [790]	2011	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.

6.10.6.1.2 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%) [791]. In more recent series, these complications appear to be less common [784, 787]. Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [787].

Table 6.10.3: Perioperative morbidity in selected SRP case series, including at least 30 patients

Reference	Year	n	Rectal injury (%)	Anastomotic stricture (%)	Clavien 3-5, %	Blood loss, mL, mean, range
Stephenson, et al. [784]	2004	100	15 vs. 2*	30	33 vs. 13*	-
Ward, et al. [792]	2005	138	5	22	-	-
Sanderson, et al. [788]	2006	51	2	41	6	-
Gotto, et al. [791]	2010	98	9	41	25	-
Heidenreich, et al. [785]	2010	55	2	11	3.6	360 (150-1450)

* SRP performed before vs. after 1993.
n = number of patients; SRP = salvage radical prostatectomy.

6.10.6.2   Summary of salvage radical prostatectomy
In general, SRP should be considered only for patients with low comorbidity, a life expectancy of at least 10 years, a pre-SRT PSA < 10 ng/mL and biopsy Gleason score ≤ 7, no lymph node involvement pre-SRT, and whose initial clinical staging was T1 or T2 [787].

6.10.7   **Salvage cryoablation of the prostate**
6.10.7.1   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 5-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 [793]. In a multicentre study reporting the current outcome of SCAP in 279 patients, the 5-year biochemical recurrence-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 [794].

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 5-year BCR-FS was 61% following SRP, significantly better than the 21% detected after SCAP. The 5-year OS was also significantly higher in the SRP group (95% vs. 85%) [795].

Table 6.10.4: Oncological results of selected SCAP case series, including at least 50 patients

Reference	Year	n	Median FU (mo)	BCR-free probability, %	Time probability, yr	Definition of failure
Pisters, *et al.* [796]	1997	150	17	44	-	Nadir + 0.2
Bahn, *et al.* [797]	2003	59	82	59	7	PSA > 0.5
Ismail, *et al.* [793]	2007	100	33	73 (low risk)	5	ASTRO
Pisters, *et al.* [794]	2008	279	22	58	5	ASTRO and Phoenix
Williams, *et al.* [798]	2011	187	7.46 yr	39	10	Nadir +2
Spiess, *et al.* [799]	2010	450	40.8	34	-	PSA > 0.5

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients.

6.10.7.2   Morbidity
According to Cespedes *et al.* [800], the risks of urinary incontinence and ED at least 12 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 [794]. With the use of third-generation technology, complications such as urinary incontinence and obstruction/retention have significantly decreased during the last decade (see Table 6.10.5) [801].

Table 6.10.5: Perioperative morbidity, erectile function and urinary incontinence in selected SCAP case series, including at least 50 patients

Reference	Year	n	Incontinence, %	Obstruction/Retention, %	Rectourethral fistula, %	ED, %
Pisters [796]	1997	150	73	67	1	72
Bahn [797]	2003	59	8	-	3.4	-
Ismail [793]	2007	100	13	4	1	-
Pisters [794]	2008	279	4.4	3.2	1.2	-
Ahmad [802]	2013	283	12	7	1.8	83

ED = erectile dysfunction; n = number of patients.

6.10.7.3   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 10 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.

*6.10.8   **Salvage brachytherapy for radiotherapy failure***
Following local recurrence after previous definitive RT there is no indication for salvage EBRT as the total dose is limited and therefore the chance of cure is low. For carefully selected patients with primary localised PCa and histologically proven local recurrence, high- or low-dose rate (HD/LDR) brachytherapy remain the effective treatment options with an acceptable toxicity profile [803-805]. However, the published series are relatively small; therefore 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 [803]. With a median follow-up of 60 months the 5-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 MSCCC in New York [806]. 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 5 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 [807].

Using LDR-brachytherapy with ^{103}Pd (palladium), long-term outcome was reported in 37 patients with a median follow-up of 86 months [804]. The biochemical control rate after 10 years was 54%. However, the crude rate of ≥ grade 2 toxicity was 46% and ≥ 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 [808].

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. Therefore salvage brachytherapy remains a treatment option for selected patients with histologically proven local recurrence after RT.

6.10.9 Salvage High-intensity focused ultrasound (HIFU)

6.10.9.1 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 6.10.6: Oncological results of selected salvage HIFU case series, including at least 20 patients

Reference	Year	n	Median FU (mo)	BCR-free probability, %	Negative biopsy rate
Colombel, *et al.* [809]	2006	224	15-18	-	80
Gelet, *et al.* [810]	2000				
Gelet, *et al.* [811]	2004				
Uchida, *et al.* [812]	2011	22	24	59 (Phoenix) (24 mo.)	92 (only 12 biopsied)
Berge, *et al.* [813]	2011	46	9	60.9 (9 mo)	

FU = follow-up; mo = months; n = number of patients.

6.10.9.2 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.

6.10.9.3 Summary of salvage high-intensity focused ultrasound (HIFU)
There is a lack of data which prohibits any recommendation regarding the indications for salvage HIFU.

6.10.10 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 5-year metastasis-free survival rate was 88% with HT vs. 92% with WW (p = 0.74) [814].

6.10.11 Salvage lymph node dissection

Novel imaging modalities improve the early detection of nodal metastases [815]. The surgical management of (recurrent) nodal metastases has been the topic of several retrospective analyses [815, 816, 817]. The majority of treated patients showed biochemical recurrence but clinical recurrence-free and cancer specific 10-year survival over 70% has been reported [818]. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [577]. Addition of RT to the lymphatic template after salvage LND may improve BCR rate [819]. No level 1 evidence is available on the effects of salvage nodal dissection on survival [820].

6.10.11.1 Guidelines for salvage lymph node dissection

Recommendation	GR
Discuss salvage lymph node dissection 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

LND = lymph node dissection.

Local salvage treatment	LE	GR
Biochemical recurrence after radical prostatectomy		
Offer patients with a PSA rise from the undetectable range and favourable prognostic factors (≤ pT3a, time to biochemical recurrence > 3 year, PSA-DT > 12 months, Gleason score ≤ 7) surveillance and possibly delayed salvage radiotherapy.	3	B
Treat patients with a PSA rise from the undetectable range with salvage radiotherapy. The total dose of salvage radiotherapy should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	2	A
Biochemical recurrence after radiotherapy		
Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage radical prostatectomy.	3	B
Due to the increased rate of side effects, perform salvage radical prostatectomy 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
Systemic salvage treatment		
Do not routinely offer 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

ADT = androgen-deprivation therapy; PSA-DT = prostate-specific antigen doubling time.

6.11   Treatment: Castration-resistant PCa (CRPC)
6.11.1   Background
Our knowledge of the mechanisms involved in the development of castration-resistant PCa (CRPC), remains incomplete [821, 822]. An alteration in normal androgen signalling is thought to be central to the pathogenesis of CRPC [823]. It is mediated through two main, overlapping, mechanisms. These are androgen receptor (AR)-independent and AR-dependent.

6.11.2   *Definition of progressing PCa after castration*

Table 6.11.1: Definition of CRPC

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;   a) Biochemical progression: Three consecutive rises in PSA 1 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) [824]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

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 2 years [825], 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 doubling time have been associated with time to first bone metastasis, bone metastasis-free and OS [825, 826]. 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 [827] suggested a bone 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 3 months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level.

The rest of this Section focuses on management of men with proven metastatic CRPC (mCRPC)

6.11.3 Assessing treatment outcome in castration-resistant PCa (CRPC)

Precise quantification of the effect of treatments on metastatic bone disease is difficult to quantify and rarely used in clinical practice. Improvements in QoL, PFS and PCa-specific survival are all used, but the gold standard remains OS [828].

6.11.3.1 PSA level as marker of response

Many contemporary studies use PSA as a marker of response, even though there is no consensus about the magnitude and duration of a decline in PSA level. Although PSA is used as a rapid screening tool to test the activity of new agents, there is conflicting evidence about the role of PSA as a surrogate marker. Trials of the vaccines sipuleucel-T (Provenge phase III) [829] and TRICOM (PROSTVAC phase II) [830] have demonstrated a significant OS benefit without any PSA change, raising questions about the value of PSA response for non-hormonal non-cytotoxic drugs [831]. In addition, wide fluctuations have been seen in PSA values due to a transient effect of drugs on PSA production. The effect of drugs on PSA expression should be considered when interpreting PSA response data, which should be viewed together with other clinical data [832-835]. Nevertheless, it has been shown reproducibly that > 30% PSA decline following therapy is associated with a significant survival advantage [836, 837]. An improved PSA response was also associated with prolonged survival in the TAX 327 study, with a median survival of 33 months when the PSA was normalised (< 4 ng/mL) vs.15.8 months for an abnormal PSA [838].

6.11.4 Androgen deprivation in castration-resistant PCa

Eventually men with PCa show evidence of disease progression despite castration. In this situation continued testicular androgen suppression in CRPC is debatable [839].

Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [840, 841]. 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 6.11.2: Randomised phase III controlled trials - first-line treatment of mCRPC*

Author	Year	Intervention	Comparison	Selection criteria	Main outcomes
DOCETAXEL					
SWOG 99-19 [842]	2004	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		<u>OS</u>: 17.52 vs. 15.6 mo. (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) <u>PFS</u>: 6.3 vs. 3.2 mo. (p < 0.001)
TAX 327 [838] [603]	2008	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		<u>OS</u>: 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 [843-845]	2013	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) Main side effects G3-4: cardiac disorders 4% in the placebo group vs. 8% on abiraterone, increased alanine aminotransferase 6% vs. <.1%, and hypertension 5% vs. 3%.
ENZALUTAMIDE					
PREVAIL Beer [846]	2014	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) Main side effects (G3-4) Hypertension (7%), fatigue (2%) and hot flushes (< 1%)
SIPULEUCEL-T					
Kantoff [830]	2010	sipuleucel-T [609]	placebo [609]	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) Main side effects outcomes: 31.7% vs. 35.1%.
Small [829]	2006	sipuleucel-T [829]	placebo [71]	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. Main side effects outcomes: 31.1% vs. 29.3% grade 3, 24.45% both groups grade 4.

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.

6.11.5 *Hormonal drugs targeting the endocrine pathways in the pre-docetaxel space*
6.11.5.1 *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 [843]. 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) [845]. Adverse events (AEs) related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1 - 2 (see Table 6.11.2 for more details).

6.11.5.2   Enzalutamide
A randomised phase III trial (PREVAIL) [846] 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, in 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 (see Table 6.11.2 for more details).

*6.11.6   **Non-hormonal therapy***
6.11.6.1   Docetaxel regimen
A significant improvement in median survival of 2-2.9 months occurred with docetaxel-based chemotherapy compared to mitoxantrone + prednisone therapy [838, 842]. The standard first-line chemotherapy is docetaxel 75 mg/m^2 3 weekly doses combined with prednisone 5 mg BID, up to 10 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 [848]. A better risk group definition was presented more recently, 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 3 significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [849]. Age by itself is not a contraindication to docetaxel [604] but attention must be paid to closer monitoring and comorbidities as discussed in Section 6.7.2.2.2.2 [850]. In men with mCRPC who are thought to be unable to tolerate the standard regime using docetaxel 50mg/m^2 every 2-weeks seems well tolerated with less Grade 3-4 adverse events and prolonged time to treatment failure although survival data are not available [851].

6.11.6.2   Vaccine
In 2010, a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [826]. 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.

Figure 6.11.1: Flowchart of the potential therapeutic options after PSA progression following hormonal therapy in metastatic patients.
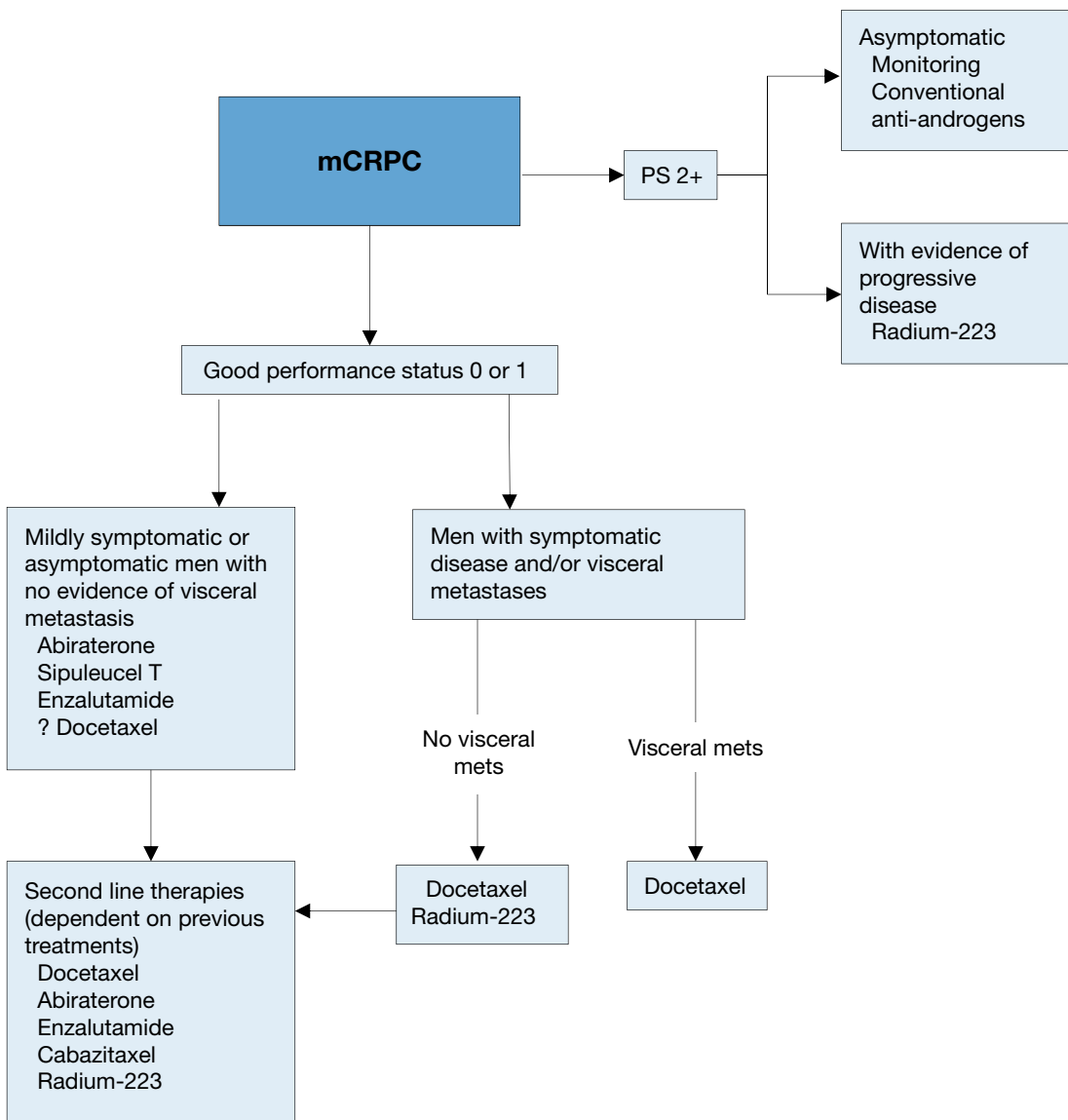
PS = performance status; mCRPC = metastatic castrate resistant prostate cancer; mets = metastases.

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 first "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 was 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 produced following the St. Gallen Consensus Conference [852] (see flowchart).

6.11.7   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 [852]. Prostate-specific antigen alone is not reliable enough for monitoring disease activity in advanced CRPC, since visceral metastases may develop in men without rising PSA [847]. Instead PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [842]. A majority of experts at a recent consensus meeting suggested regular review and repeat blood profile every 2-3 months with bone

scintigraphy and CT scans at least every 6 months even in the absence of a clinical indication [852]. 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.

6.11.8   Treatment after first-line docetaxel for mCRPC

All patients who receive docetaxel-based chemotherapy for mCRPC will eventually progress. A number of clinical trials investigated the role of further chemotherapy. Intermittent docetaxel re-treatment in patients who had clearly responded to first-line docetaxel showed a PSA response in about 60% with a median time to progression of about 6 months, while treatment-associated toxicity was minimal and similar to that of first-line docetaxel [853, 854]. No survival improvement has been demonstrated with docetaxel rechallenge in responders. All treatments in this setting are presented in Table 6.11.3.

Table 6.11.3: Randomised controlled phase III - second-line trials for mCRPC*

Author	Year	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE					
Fizazi [608]	2012	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. Radiologic PFS: no change Main side-effects outcomes: Similar.
de Bono [605]	2011				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. Main side-effects outcomes: Adverse events related to mineralocorticoid excess with abiraterone.
RA -223					
Parker [855]	2013	RA 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 Main side-effects outcomes: 56% vs. 62% grade 3-4.
CABAZITAXEL					
Bahl [611]	2013	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: 2 years. PFS: - Main side-effects outcomes: Similar.
deBono [607]	2010				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) Main side-effects outcomes: 82% vs. 58% neutropenia.

ENZALUTAMIDE					
Scher [606]	2012	enzalutamide	placebo	Previous docetaxel. ECOG 0-2.	<u>OS</u>: 18.4 vs. 13.6 mo. (p < 0.001 HR: 0.63, 95% CI: 0.53-0.75). FU: 14.4 mo. <u>Radiologic</u> PFS: 8.3 vs. 2.9 mo. HR: 0.40, 95% CI: 0.35-0.47 p < 0.0001) <u>Main side-effects outcomes</u>: 45.3% vs. 53.1% grade 3-4.

Only studies reporting survival outcomes as primary endpoints have been included.
OS = overall survival; PFS = progression-free survival.

6.11.8.1   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 [607]. Patients received a maximum of 10 cycles of cabazitaxel (25 mg/ m^2) or mitoxantrone (12 mg/m^2) plus 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 [828]. This drug 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 [856].

6.11.8.2   Abiraterone acetate

Positive preliminary results of the large phase III COU-AA-301 trial were reported after a median follow-up of 12.8 months [605] and the final results have been reported more recently [608]. A total of 1,195 patients with mCRPC were randomised 2:1 to abiraterone acetate plus prednisone or placebo plus 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 side effects 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).

6.11.8.3   Enzalutamide

The planned preliminary analysis of the AFFIRM study was published in 2012 [606]. 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 2 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.

6.11.8.4   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. In general subsequent treatments can be expected to have a smaller response [857, 858] with evidence of cross-resistance between enzalutamide and abiraterone [859].

6.11.9   Bone targeted therapies 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 [860]. 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.

6.11.9.1   Common complications due to bone metastases
Common complications due to bone metastases include bone pain, vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation is an effective treatment for painful spinal fracture, whatever its origin, clearly improving both pain and QoL [861]. However, it is still important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [862, 863]. 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 external beam irradiation [864]. Otherwise, EBRT, with or without systemic therapy, is the treatment of choice.

6.11.9.2   Painful bone metastases
Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective [865], even as a single fraction [866].

6.11.9.2.1 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 RA-223 or placebo, plus standard of care. The primary end-point was OS. RA-223 significantly improved median OS by 3.6 months (HR: 0.70; p < 0.001) [855]. 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 RA-223, this did not differ significantly from that in the placebo arm [855]. Radium-223 was effective and safe no matter if the patients were docetaxel pretreated, or not [867].

6.11.9.2.2 Bisphosphonates
Zoledronic acid has been used in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anticancer treatments but docetaxel was available. 643 patients who had CRPC [868] with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every 3 weeks for 15 consecutive months, or placebo. The 8 mg dose was poorly tolerated so reduced to 4 mg but did not show a significant benefit. However, at 15 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.
          The toxicity (e.g., jaw necrosis) of these drugs, especially aminobisphosphonate, must always be kept in mind [864, 865]. Patients should have a dental examination before starting bisphosphonate therapy. The risk of jaw necrosis is increased by a history of trauma, dental surgery or dental infection, as well as long-term intravenous bisphosphonate administration [869]. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.11.9.2.3 RANK ligand inhibitors
Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κB 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) [684]. 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 [870].
          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 [684].

6.11.10   Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant PCa

Summary of evidence	LE
No definitive strategy regarding 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 or chemotherapy) as no clear predictive factors exist.	3

Recommendation	LE	GR
Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing CRPC.	4	A
Do not treat patients for <u>non-metastatic</u> CRPC outside of a clinical trial.	3	A
Counsel, manage and treat patients with mCRPC in a multidisciplinary team.	3	A
In men treated with maximal androgen blockade, stop anti-androgen therapy once PSA progression is documented. *Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.*	2a	A
Treat patients with mCRPC with life prolonging agents. Base the choice of first line treatment on the performance status, symptoms, comorbidities and extent of disease (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).	1b	A

CRPC = castration-resistant PCa.

*6.11.11   **Guidelines for cytotoxic treatment in castrate-resistant PCa***

Recommendation	LE	GR
In <u>non-metastatic</u> CRPC, offer cytotoxic therapy only in a clinical trial setting.	3	B
Counsel, manage and treat patients with mCRPC in a multidisciplinary team.	3	A
Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m^2 every 3 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

mCRPC = metastatic castration-resistant PCa.

*6.11.12   **Guidelines for supportive care of castrate-resistant PCa***

These recommendations are in addition to appropriate systemic therapy.

Recommendation	LE	GR
Offer bone protective agents to patients with skeletal metastases to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, and jaw necrosis in particular must be avoided.	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, radionuclides, 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 BT, 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. 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 and this 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 [871, 872]. 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 $\geq$ 0.2 ng/mL [873]. However, others have argued for a higher cut-off of 0.4 ng/mL for patients at high risk of clinical progression [872].

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 [874]. 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 5 years [875]. 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 [710]. It applies to patients with or without HT.

After HIFU or cryotherapy, there are various definitions for PSA relapse [506]. Most of these are based on a cut-off PSA level of ~1 ng/mL, combined with negative post-treatment biopsy. No endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of BCF.

7.1.3.3 Prostate-specific antigen monitoring after radical prostatectomy

Prostate-specific antigen is expected to be undetectable within 6 weeks after successful RP [876]. Persistently elevated PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual pelvic disease.

A rapidly increasing PSA level indicates distant metastases, whereas a later, slowly increasing, level most likely indicates local recurrence. Time to PSA recurrence and tumour differentiation are important predictive factors distinguishing local and systemic recurrence [877]. Local treatment failure and distant metastases occur with undetectable PSA levels. This is rare and occurs mostly in patients with undifferentiated tumours [878].

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 [879], although the optimal value is controversial. The interval before reaching the nadir can be up to 3 years or more. Biochemical failure after RT is currently defined as PSA > 2 ng/ mL above the nadir [710]. After RT, PSA-DT is correlated with site of recurrence: patients with local recurrence have a doubling time of 13 months compared to 3 months for those with distant failure [880].

7.1.3.5 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level [878]. However, this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. PSA 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) [881].

7.1.3.6 Transrectal ultrasound, bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and ^{11}C-choline positron emission tomography computed tomography (PET/CT)

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 6.19.4 for a more detailed discussion).

7.1.3.6.1 Transrectal ultrasonography/magnetic resonance imaging biopsy

Biopsy of the prostate bed and urethrovesical anastomosis 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. PSA measurement, disease-specific history and DRE are recommended at 3, 6 and 12 months post-operatively, every 6 months thereafter until 3 years, and then annually.

The first clinic visit is mainly to detect 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 PSA level > 0.2 ng/mL is associated with residual or recurrent disease.	
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.	B
Palpable nodules and increasing serum PSA are signs of local recurrence.	B

Recommendation	GR
Routinely follow-up asymptomatic patients, by obtaining a disease-specific history and serum PSA measurement supplemented by DRE. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 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

DRE = digital rectal examination; PSA = prostate-specific antigen.

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 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 upmost 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 (see Section 6.6.2), in locally advanced and metastatic PCa [882], as in salvage ADT for relapse following treatments with curative intent [883].

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 3 months of ADT is independently associated with a shorter progression-free and OS rate [884] and might explain significant fatigue. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis [885]. 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 [214].
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 [842], 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 (< 1 nmol/L). 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 [522], known as the 'acute on-chronic effect' or 'breakthrough response'.
The timing of measurements is not clearly defined. A 3 to 6-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 7.5). The patient's general

practitioner should probably be more involved.

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 6.8.7.1.3.1). It is suggested that routine bone monitoring should be performed every 2 years during castration [886], or yearly if there are other risk factors [887, 888]. 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 [884, 885]. 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 3 - 6 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 3-6 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*

Recommendation	GR
Evaluate patients at 3 - 6 months after the initiation of treatment.	A
As a minimum, tests should include serum PSA measurement, 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 6 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 3 to 6 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, CRPC requires a testosterone level < 50 ng/mL (< 1 mL/L).	B
Do not offer routine imaging to otherwise stable patients.	B

CRPC = castrate-resistant PCa; DRE = digital rectal examination; PSA = prostate-specific antigen.

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9.   CONFLICT OF INTEREST

EAU Guidelines on
Renal Cell Carcinoma

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**European
Association
of Urology**

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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 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.

1.2   Panel composition
The RCC panel is an international group of clinicians consisting of urological surgeons, an oncologist, methodologists, a pathologist and a radiologist, with particular expertise in the field of urological 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/.

The panel is most grateful for the methodological and scientific support provided by the following individuals in specific parts of the guideline document:
*   Prof.Dr. O. Hes, pathologist, Plzen (CZ) (Section - Other renal tumours);
*   Dr. M. Lardas, Aberdeen (UK) and Dr. F. Stewart, Aberdeen (UK)
    (Systematic review - Tumour thrombus);
*   Dr. Christina Vogel, Munich (DE) and Prof.Dr. A. Graser, radiologist, Munich (DE)
    (Systematic review - Diagnostic imaging of RCC).

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 assessed 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 2016 RCC Guidelines document presents an update of the 2015 publication.

1.4.2   Summary of changes
All chapters of the 2016 RCC Guidelines have been updated, based on the 2015 version of the guideline. Conclusions and recommendations have been rephrased and added to, throughout the current document.

Key changes for the 2016 print:

*   Chapter 3 - Epidemiology, Aetiology and Pathology: the new Vancouver histological classification has been included.
*   Section 7.4.3.1 - Tyrosine kinase inhibitors - A new figure has been included. (Figure 7.1: Recommendations for patients with metastatic clear cell-RCC who have failed one or more lines of VEGF targeted therapy).

New data and recommendations have been included in the following sections.

3.4 Summary of evidence and recommendations for the management of other renal tumours

Recommendations	GR
In AML > 3 cm not requiring surgical intervention, medical treatment with everolimus can be considered.	C
Treat all tumours with the radiologic appearance of RCC in the same way.	C

AML = angiomyolipoma.

7.2.5.1 Summary of evidence and recommendation for adjuvant therapy

Summary of evidence	LE
Adjuvant sunitinib or sorafenib do not improve disease-free and overall survival after nephrectomy.	1b

Recommendation	GR
Adjuvant therapy with sunitinib or sorafenib should not be given.	A

7.3.2.4 Embolisation of metastases

Recommendation	GR
Stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases may be offered for local control and symptom relief.	C

7.4.1.1 Summary of evidence and recommendation for systemic therapy for advanced/metastatic RCC

Summary of evidence	LE
In mRCC, chemotherapy is otherwise not effective.	3

mRCC = metastatic renal cell carcinoma.

7.4.2.5 Summary of evidence and recommendation for immunotherapy in mRCC

Summary of evidence	LE
IFN-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in mRCC.	1b
Nivolumab leads to superior OS compared to everolimus in patients failing one or two lines of VEGF-targeted therapy.	1b

Recommendation	GR
Nivolumab is strongly recommended after one or two lines of VEGF-targeted therapy in mRCC.	A

INF = interferon; mRCC = metastatic renal cell carcinoma; mTOR = mammalian target of rapamycin inhibitor; OS = overall survival: VEGF = vascular endothelial growth factor.

7.4.6.3 Summary of evidence and recommendations for systemic therapy in mRCC

Summary of evidence	LE
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 in patients failing one or more lines of VEGF-targeted therapy.	1b

Recommendations	GR
Cabozantinib should be given for ccRCC patients who progressed after one or two lines of VEGF-targeted therapy based on a PFS advantage over everolimus.	A
Nivolumab is strongly recommended for ccRCC patients who progressed after one or two lines of VEGF-targeted therapy based on and OS advantage over everolimus.	A
Axitinib can be given as second-line treatment for mRCC after cytokines or first-line VEGF where other drugs are not safe, tolerable or available.	A
Sunitinib or everolimus can be given as first-line therapy for non-clear cell mRCC.	B

ccRCC = clear-cell renal cell carcinoma; mRCC = metastatic renal cell carcinoma; OS = overall survival: PFS = progression-free survival; VEGF = vascular endothelial growth factor.

2. METHODS

2.1 Data identification

For the 2016 Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature for the majority of chapters in the guideline as listed in Table 2.1.

A broad and comprehensive scoping exercise covering all areas of the entire guideline was performed. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews (SRs) 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 during the period from 1st January 2013 to 30th July 2015. Databases covered by the search included Medline, EMBASE, and the Cochrane Library. A total of 1,602 unique records were identified, retrieved and screened for relevance. The search strategy has been published online: http://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 guideline panel. These reviews were performed using standard Cochrane SR methodology http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

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 [3]. 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 as the above address.

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	Chapters 5.2 and 5.3 were updated by way of a SR [4]. 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 were updated by a SR. The remainder of the chapter was updated using a structured literature assessment.

Treatment of localised disease: For 2015 this section was updated by means of a SR mostly based on a literature search from 2000. A new section, 'Management of RCC with venous thrombus' has been added which is based on a SR [5].

Systemic therapy for metastatic disease: For 2015, these sections were 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 2016 update:
- What is the best surgical treatment option for clinical ≥ T2, N0M0 tumours? What is the best way of performing this procedure?
- What is the best treatment for advanced/metastatic non-clear cell RCC?
- Performance of CT for the initial diagnosis of suspected renal masses.

2.2 Review
The following section was peer reviewed prior to publication:
- Chapter 7 – Disease management.

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 Panel aim 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 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 6 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 goals for this project.

The results of ongoing and new SRs will be included in the 2017 update of the RCC Guidelines.

Ongoing systematic reviews:
- What is the best treatment option for T1a tumours? (updated).
- What is the best treatment option for T1b-T2b tumours? (updated).
- What are indications for treatment of angiomyolipoma?
- Systematic review and meta-analysis of systemic therapy of renal tumours?
- Imaging following treatment, covering the following subquestions:
  - Post surgical surveillance for either localised disease or locally advance disease;
  - Post-systemic therapy.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1   Epidemiology

Renal cell carcinoma (RCC) represents 2-3% of all cancers [6], 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, although a continuing decrease has been observed in Denmark and Sweden [7]. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney cancer-related deaths in the European Union [8]. In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilised or declined thereafter [9]. 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 [9].

Different RCC types have specific histopathological and genetic characteristics [10]. There is a 1.5:1 male predominance, with a peak incidence between 60 and 70 years. Aetiological factors include smoking, obesity [11], hypertension, acetaminophen and non-aspirin nonsteroidal anti-inflammatory drugs [12], and viral hepatitis [13-17]. Having a first-degree relative with kidney cancer also increases the risk of RCC [18]. A number of other factors associated with higher or lower RCC risk include specific dietary habits and occupational exposure to specific carcinogens, however, literature results are inconclusive [19, 20]. Moderate alcohol consumption appears to have a protective effect for unknown reasons [21, 22], as do cruciferous vegetables [23]. 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 [24-26].

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	GR
For the most important primary prevention of for RCC, eliminate cigarette smoking and reduce weight.	B

3.2   Histological diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2004 World Health Organization (WHO) classification [27] and modified by the International Society of Urological Pathology (ISUP) Vancouver Classification [28]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC - type I and II) and chromophobe (chRCC). RCC type classification has been confirmed by cytogenetic and genetic analyses [29-31] (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 perirenal fat. Fuhrman nuclear grade has been the most widely accepted grading system [32]. At the ISUP conference, a simplified, nuclear grading system, based only on size and shape of nucleoli, was proposed which will replace the Fuhrman grading system [28].

3.2.1   Clear cell (ccRCC)

Overall, ccRCC is well circumscribed, capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. The Fuhrman nuclear grading system is generally used [32]. Loss of chromosome 3p and mutation of the VHL (von Hippel-Lindau) gene at chromosome 3p25 are frequently found. ccRCC has a worse prognosis compared with pRCC and chRCC [33, 34] even after stratification for stage and grade [35]. The 5-year cancer specific survival (CSS) rate was 91%, 74%, 67% and 32% for TNM stages I, II, III and IV (patients treated 1987-98) [36]. The indolent variant of ccRCC is multilocular cystic and accounts for approximately 4% of all ccRCC [28].

3.2.2 Papillary (pRCC)

Macroscopically, pRCC is well circumscribed with pseudocapsule, yellow or brown in colour, and a soft structure. Genetically, pRCC shows trisomies of chromosomes 7 and 17 and the loss of chromosome Y. Papillary RCCs are heterogeneous, with three different subtypes; two basic (1 and 2) and a third oncocytic type. Compared with ccRCC, pRCC has a significantly higher rate of organ confined tumour (pT1-2N0M0) and higher 5-year CSF [37]. Prognosis of pRCC type 2 is worse than for type 1 [38-40]. Exophytic growth, pseudonecrotic changes and pseudocapsule are typical signs of pRCC type 1. Pseudocapsules and extensive necrotic changes cause a spherical tumour in the extrarenal section. Tumours with massive necroses are fragile and vulnerable to spontaneous rupture or rupture resulting from minimal trauma followed by retroperitoneal bleeding. A well-developed pseudocapsule in pRCCs type 1 probably prevents these tumours from rupturing despite necroses. Necroses cohere with a hypodense central area of tumour on post-contrast CT. This area is surrounded by vital tumour tissue, seen as a serpiginous contrast-enhancing margin on CT [41]. Some authors consider type 3; oncocytic pRCC, to have no pseudocapsule or massive necrosis, rare extrarenal growth and low malignant potential [40], although this type is not generally accepted [28].

3.2.3 Chromophobe (chRCC)

Overall, chRCC is a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Instead of the Fuhrman grading system, a special histopathological grading system by Paner *et al.* was proposed in 2010 [42, 43]. Loss of chromosomes 2, 10, 13, 17 and 21 are typical genetic changes [44]. The prognosis is relatively good, with high 5-year recurrence-free survival, CSS and 10-year CSS [45].

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, and a group of unclassified carcinomas. A summary of these tumours are given 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). RCCs of native end-stage kidneys are found in about 4% of patients. Their lifetime risk of developing RCCs is at least 10 times higher than in the general population. Compared with sporadic RCCs, ACKDs generally are multicentric and bilateral, found in younger patients (mostly male), and are less aggressive [46, 47]. The relatively indolent outcome of tumours in ESKD is due to the mode of diagnosis and a specific ACKD related molecular pathway still to be determined [47]. Although the histological spectrum of ACKD tumours is similar to that of sporadic RCC, the predominant form is pRCC. The remaining tumours are mostly ccRCC [46-48]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) [28].

3.3.2 Papillary adenoma

These tumours have papillary or tubular architecture of low nuclear grade and are 5 mm in diameter or smaller [27]. They are found incidentally in nephrectomy specimens.

3.3.3 Hereditary kidney tumours

Hereditary kidney tumours are found in the following entities: VHL syndrome, hereditary pRCC, Birt-Hogg-Dubé syndrome (see Hybrid oncocytoma-chromophobe carcinoma), hereditary leiomyomatosis and renal cell cancer (HLRCC), tuberous sclerosis complex, germline succinate dehydrogenase (SDH) mutation, non-polyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, phosphatase and tensin homolog (PTEN) harartoma syndrome (PHTS), constitutional chromosome 3 translocation, and familial non-syndromic ccRCC. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [27, 28, 38, 49].

3.3.4 Angiomyolipoma

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically, and is four times more likely in women. It also occurs in tuberous sclerosis (TS). It 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 TS in lymph nodes (LNs), but is not metastases, and has a multicentric genesis. Angiomyolipoma can be due to angiotrophic-type growth in the renal vein or the IVC. Angiomyolipoma with LN involvement and tumorous thrombus is benign. Only epithelioid AML is potentially malignant [27, 50]. Angiomyolipoma has a slow and consistent growth rate, and minimal morbidity [51]. The main complications of renal AML are retroperitoneal bleeding or bleeding

into the urinary collection system, which can be life-threatening [52]. The bleeding tendency is related to the angiogenic component of the tumour that includes irregular and aneurysmatic blood vessels [52]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of TS [52, 53]. 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 [51, 54] (LE: 3). Risk factors for delayed intervention include tumour size ≥ 4 cm and symptoms at diagnosis [54]. Selective arterial embolisation seems to be the first-line option used for active treatment after AS was discontinued [54] (LE: 3). Selective arterial embolisation (SAE) is an efficient treatment for AML devascularisation but only for volume reduction [55]. And although SAE controls haemorrhage in the acute setting, it has limited value in the longer-term [56, 57]. If surgery is selected, most cases of AML can be managed by conservative nephron-sparing surgery (NSS), although some patients may require complete nephrectomy [53] (LE: 3). Radiofrequency ablation (RFA) can be an option as well [51, 52, 58]. The volume of AML can be reduced by the mTOR inhibitor everolimus [59]. A clinical phase II trial and its open-label extension of medical management with the mTOR inhibitor everolimus in AML, not requiring surgical intervention showed a response rate of 81.6 (64.5%) (≥ 50% or 30% tumour's volume reduction) by week 96, confirming the long-term safety profile of everolimus [59]. Sirolimus can be combined with deferred surgery [60].

Table 3.1: Other renal cortical tumours, and recommendations for treatment (GR: C)

Entity [27, 28]	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, option of gemcitabine plus doxorubicin [61].
Multilocular clear cell RCC		Low, no metastasis	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 in CSS in comparison with ccRCC is 4.49 [34].	High, very aggressive. Median survival 30 months [62].	Surgery/Response to targeted therapies was poor [63].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is 5 months [62].	Surgery/different chemotherapy regimens, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients under 40, more common in females. It constitutes with TRCC 6p21 MiT translocation RCCs [64].	High	Surgery/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 (tubulo) pRCC	It has been reported under the term renal angiomyomatous tumour (RAT) as well.	Low	Surgery, NSS
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS
Hybrid oncocytic chromophobe tumour	Mixture of cells of chRCC and renal oncocytoma. Three clinicopathological situations: sporadic, in association with renal oncocytosis/oncocytomatosis or in patients with Birt-Hogg-Dubé syndrome.	Low or benign	Surgery, NSS

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 [65, 66].	Benign	Observation (when histologically confirmed) [67, 68]/NSS.
Hereditary kidney tumours	Details see above.	High	Surgery, NSS
Angiomyolipoma	Details see above.	Benign	Consider treatment only in very well selected patients.
Carcinoma associated with neuroblastoma	Long-term survivors of childhood neuroblastoma have a 329-fold increased risk of renal carcinoma.	Variable	Surgery, NSS
Thyroid-like follicular carcinoma of the kidney (TLFC)	Succinate Dehydrogenase B Mutation-associated RCC, ALK Translocation RCC (ALK - anaplastic lymphoma kinase).	Low	Surgery, NSS
Unclassified RCC	RCC that cannot be assigned to any other category of RCC-type carcinoma [27].	Variable	Surgery, NSS

CSS = cancer specific survival; NSS = nephron-sparing surgery; VEGF = vascular endothelial growth factor.

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

Summary of evidence	LE
Except for AML, most other renal tumours cannot be differentiated from RCC by radiology.	3
Biopsy-proven oncocytomas are benign lesions.	3
In advanced uncommon renal tumours, a standardised oncological treatment approach does not exist.	3

Recommendations	GR
Bosniak cysts ≥ type III should be regarded as RCC and treated accordingly. Treat Bosniak type III or IV cysts the same as RCC.	C
Treat most AMLs with active surveillance. Treat with selective arterial embolisation or NSS for: • large tumours (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.	C
In AML > 3 cm not requiring surgical intervention, medical treatment with everolimus can be considered.	C
Treat all tumours with the radiologic appearance of RCC in the same way.	C
Offer watchful waiting to patients with biopsy-proven oncocytomas.	C

For advanced uncommon renal tumours, develop individualised oncological treatment plans for each patient.	C

AML = angiomyolipoma; NSS = nephron-sparing surgery.

4.   STAGING AND CLASSIFICATION SYSTEMS

4.1   Staging

The TNM classification system is recommended for clinical and scientific use [69], but requires continuous improvements [70]. The latest version was published in 2009 with a supplement published in 2012 (Table 4.1), and its prognostic value was confirmed in single and multi-institution studies [71, 72]. 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 [73].
- Since the 2002 version, tumours with renal sinus fat invasion have been classified as pT3a.
- However, renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion but is included in the same pT3a stage group [74-76] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [72].
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [77, 78] (LE: 4).

Table 4.1: 2009 TNM classification system [69] **and TNM supplement 2012** [79]

T - Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm in greatest dimension, limited to the kidney		
	T1a	Tumour ≤ 4 cm in greatest dimension, limited to the kidney	
	T1b	Tumour > 4 cm but ≤ 7 cm in greatest dimension	
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
	T2a	Tumour > 7 cm but ≤ 10 cm in greatest dimension	
	T2b	Tumours > 10 cm limited to the kidney	
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland or beyond Gerota's fascia		
	T3a	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or invades perirenal and/or renal sinus fat (peripelvic), but not beyond Gerota's fascia	
	T3b	Tumour grossly extends into the vena cava (VC) below the diaphragm	
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the VC	
T4	Tumour invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)		
N - Regional LNs			
NX	Regional LNs cannot be assessed		
N0	No regional LN metastasis		
N1	Regional LN metastasis		
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
Stage IV	T1, T2, T3	N1	M0
	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 and the C-index have been proposed, to standardise the description of renal tumours [80-82]. These systems include assessment of tumour size, exophytic/endophytic properties, nearness to the collecting system and renal sinus, and anterior/posterior 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 best 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 used to investigate various non-specific symptoms and other abdominal diseases [72, 83] (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 [84, 85] (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 [86] (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 [87, 88], 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 [89, 90] (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 [83] (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 [91] (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 [92-94] (LE: 3).

5.2.2   **CT or MRI**

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 15 or more HUs demonstrates enhancement [95] (LE: 3). To maximise differential diagnosis and detection, the evaluation should include images from the nephrographic phase for best depiction of renal masses, which do not enhance to the same degree as the renal parenchyma. CT or MRI allow accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [65, 96-98] (LE: 3). Abdominal CT provides information on:
- Function and morphology of the contralateral kidney [99] (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 biphasic CT angiography is useful in selected cases for detailed information on renal vascular supply [100, 101].

If the results of CT are indeterminate, MRI may provide additional information on:
- Enhancement in renal masses [102];
- Locally advanced malignancy [103-105];
- Venous involvement if the extent of an inferior vena cava (IVC) tumour thrombus is poorly defined on CT [103-106] (LE: 3). Doppler US is less accurate for identifying the extent of a venous tumour thrombus (VTT) [105] (LE: 3).

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [104, 107] (LE: 3). Advanced MRI techniques such as diffusion-weighted and perfusion-weighted imaging are being explored for renal mass assessment [108].

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 [89, 90] (LE: 2a).

The value of positron-emission tomography (PET) in the diagnosis and follow-up of RCC remains to be determined, and PET is not currently recommended [109] (LE: 3).

5.2.4   **Radiographic investigations for metastatic RCC**

Chest CT is accurate for chest staging [77, 78, 110-112] (LE: 3). However, routine chest radiography must be performed for metastases, but is less accurate than chest CT (LE: 3). There is a consensus that most bone and brain metastases are symptomatic at diagnosis, thus routine bone or brain imaging is not generally indicated [110, 113, 114] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [113, 115, 116] (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 [117, 118] (LE: 3). This system also advocates treatment for each category (Table 5.1).

Table 5.1: Bosniak classification of renal cysts [117]

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. 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 should be considered for active surveillance in select patients with 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 [119-124] (LE: 3). 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 [121, 123] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [119-123, 125] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [119-123] (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 [4]. Other studies showed that solid pattern and larger tumour size are predictors of a diagnostic core biopsy [121, 123] (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 [4] (LE: 2b). However, 0-22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [119-126] (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%) [123, 127-129].

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 partial or radical nephrectomy (RN) was 90.3% in the pooled analysis [4].

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) [4] (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 [121, 123, 130, 131] (LE: 4). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [132] (LE: 2b).

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) [4, 121, 123] (LE: 2b).

Combined FNA and core biopsies can provide complementary results, especially for complex cystic lesions [122, 126, 127, 133, 134] (LE: 3).

Overall, percutaneous biopsies have a low morbidity [4]. Tumour seeding along the needle tract is anecdotal. Spontaneously resolving subcapsular/perinephric haematoma 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 [4].

5.4 Recommendations for the diagnostic assessment of renal cell carcinoma

Recommendations	GR
Contrast-enhanced multi-phasic abdominal CT and MRI are recommended for the work-up of patients with RCC and are considered equal both for staging and diagnosis.	B
Contrast-enhanced multi-phasic abdominal CT and MRI are the most appropriate imaging modalities for renal tumour characterisation and staging prior to surgery.	C
A chest CT is recommended for staging assessment of the lungs and mediastinum.	C
Bone scan is not routinely recommended.	C
Renal tumour biopsy is recommended before ablative therapy and systemic therapy without previous pathology.	C
Percutaneous biopsy is recommended in patients in whom active surveillance is pursued.	C
Obtain percutaneous renal tumour biopsy with a coaxial technique.	C

CT = computed tomography; MRI = magnetic resonance imaging.

6. PROGNOSTIC FACTORS

Prognostic factors can be classified into: anatomical, histological, clinical, and molecular.

6.1 Anatomical factors
Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [69] (Table 4.1).

6.2 Histological factors
Histological factors include Fuhrman grade, RCC subtype, sarcomatoid features, microvascular invasion, tumour necrosis, and invasion of the collecting system. Fuhrman nuclear grade is the most widely accepted grading system [32]. Although affected by intra- and inter-observer discrepancies, Fuhrman nuclear grade is an independent prognostic factor [135]. A simplified two- or three-strata system may be as accurate for prognostication as the classical four-tiered grading scheme [136, 137] (LE: 3). In univariate analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [138, 139]. However, prognostic information provided by the RCC type is lost when stratified to tumour stage [33, 139] (LE: 3).

Differences in tumour stage, grade and cancer specific survival (CSS) between the RCC types are illustrated in Table 6.1.

Table 6.1: Basic characteristics of three main types of RCC [33, 34, 140]

Type	Percentage of RCC (~)	Advanced disease at diagnosis (T3-4, N+, M+)	Fuhrman Grade 3 or 4 [32]	CSS (HR)
ccRCC	80-90%	28%	28.5%	referent
pRCC	6-15%	17.6%	28.8%	0.64 - 0.85
chRCC	2-5%	16.9%	32.7%*	0.24 - 0.56

* The Fuhrman grading system is validated for ccRCC, but is unreliable for chRCC. Data based on the Paner et al. grading system are not available yet [32, 42, 43].
CSS = cancer-specific survival; HR = hazard ratio.

In all RCC types, prognosis worsens with stage and histopathological grade (Tables 6.2 and 6.3). The 5-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 inhibitor (TKI) [141]. Sarcomatoid changes

can be found in all RCC types and are equivalent to high grade and very aggressive tumours.

Table 6.2: CSS by stage and histopathological grade in RCCs - hazard ratio (95% CI) [34]**).**

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.

Long-term survival in RCC patients treated by radical (RN) or partial nephrectomy (PN) between 1970 and 2003; for unilateral, sporadic ccRCC, pRCC or chRCC in a cohort study [140] (Table 6.3).

Table 6.3: CSS of surgically treated patients by RCC type (estimated survival rate in percentage [95% CI])

Survival time	5 years (%)	10 years (%)	15 years (%)	20 years (%)
ccRCC	71 (69-73)	62 (60-64)	56 (53-58)	52 (49-55)
pRCC	91 (88-94)	86 (82-89)	85 (81-89)	83 (78-88)
chRCC	88 (83-94)	86 (80-92)	84 (77-91)	81 (72-90)

Two subgroups of pRCC with different outcomes have been identified [142]: Type 1 are low-grade tumours with a chromophilic cytoplasm and a favourable prognosis. Type 2 are mostly high-grade tumours with an eosinophilic cytoplasm and a propensity for metastases (LE: 3).

RCC with Xp 11.2 translocation has a poor prognosis [143]. Its incidence is low, but should be systematically addressed in young patients.

RCC type classification has been confirmed by cytogenetic and genetic analyses [29-31] (LE: 2b).

6.3 Clinical factors

These include performance status (PS), localised symptoms, cachexia, anaemia, platelet count, neutrophil count, and neutrophil-to-lymphocyte ratio [86, 144-147] (LE: 3).

6.4 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [148], PTEN (phosphatase and tensin homolog) (cell cycle), E-cadherin, C-reactive protein (CRP), osteopontin [149] and CD44 (cell adhesion) [150, 151], CXCR4 [152], and other cell cycle and proliferative markers [56, 153] have been investigated (LE: 3). None of these markers have clearly improved the predictive accuracy of current prognostic systems, none have been externally validated, and their use is not recommended in routine practice. Although gene expression profiling seems promising, it has not identified new relevant prognostic factors [154].

6.5 Prognostic systems and nomograms

Post-operative prognostic systems and nomograms combining independent prognostic factors have been developed and externally validated [155-161]. 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 histo-prognostic schemes [162]. Recently, new pre-operative nomograms with excellent PAs have been designed [163, 164]. Table 6.4 summarises the current most relevant prognostic systems.

6.6 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, Fuhrman nuclear grade, and RCC subtype (WHO, 2004; [165]) provide important prognostic information.	2

Recommendations	GR
Use the current TNM classification system.	B
Use grading systems and classify RCC subtype.	B
Use prognostic systems in the metastatic setting.	B
In localised disease, the use of integrated prognostic systems or nomograms is not routinely recommended, although they can provide a rationale for enrolling patients into clinical trials.	C
Molecular prognostic markers are not recommended for routine clinical use.	C

TNM = Tumour, Node, Metastasis (classification); WHO = World Health Organization.

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	x						
	Post-operative Karakiewicz's nomogram	x			x	x		x						
Metastatic RCC	MSKCC prognostic system			x					x	x	x	x		
	Hang's model			x					x	x	x	x	x	x

ECOG-PS = Eastern Cooperative Oncology Group - performance status; 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 through 7.2.4.2. This review included all relevant published literature comparing surgical management of localised RCC (T1-2N0M0) [166, 167]. Randomised or quasi-randomised controlled trials (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. For this Guidelines version, an updated search was performed (see Methods section 2.1 for details).

7.1.2   *Surgical treatment*

7.1.2.1   *Nephron-sparing surgery versus radical nephrectomy*

Based on current available oncological and quality of life (QoL) outcomes, localised renal cancers are better managed by NSS (PN) rather than RN, irrespective of the surgical approach.

The estimated CSS rates at 5 years were comparable using these surgical techniques [168-172]. This was recently confirmed in a study of solitary T1-2 N0M0 renal tumours ≤ 5 cm with normal contralateral kidney function and WHO PS 0-2. At 9.3 years survival follow-up, 198 patients were alive after RN and 173 after PN. The CSS was 98.5 vs 97%, respectively. Local recurrence occurred in one and 6 patients in the RN and PN group, respectively [173].

A number of studies compared PN vs. RN (open or laparoscopic) for renal carcinoma (≤ 4 cm) [173-177]. RN was associated with increased mortality from any cause after adjusting for patient characteristics. In a prematurely closed randomised study of RCC ≤ 5 cm, comparing PN and RN, there was no difference in OS in the targeted population [172]. In studies analysing RCCs of 4-7 cm, no differences in CSS was observed between PN and RN [176, 178-185]. When laparoscopic PN was compared with laparoscopic RN in RCCs > 4 cm, there was no difference in OS, CSS and recurrence-free survival (RFS) rates [186]. Furthermore, a retrospective matched-pair analysis in elderly patients [187] reported a CSS of 98% for PN vs. 95% for RN. Other studies have compared various aspects of QoL and safety in open PN and RN [168, 169, 171, 183, 185, 188-190].

There was no difference in the length of hospital stay [169, 170, 189], blood transfusions [169, 189, 190], or mean blood loss [169, 189]. Complication rates were inconsistently reported and one intervention was not favoured over another [191]. One study found that mean operative time was longer for open PN [191], but other research found no difference [192]. Three studies consistently reported worse renal function after RN compared to PN [168, 171]. More patients had impaired post-operative renal function after RN after adjustment for diabetes, hypertension and age [171].

One database review compared open PN with laparoscopic RN in RCCs 4-7 cm. A significantly lower mean increase in post-operative creatinine levels was found [179]. Another study comparing laparoscopic PN vs. laparoscopic RN found that estimated GFR (eGFR) decreased less in the PN group, while the RN group had significantly more patients with a two-stage increase in ACKD [186]. Another database review [193] compared safety and efficacy of laparoscopic PN in RCCs > 2 cm (2-4 cm vs. > 4 cm). The laparoscopic PN group had a greater post-operative decrease in eGFR compared to the patients with smaller RCCs.

Two studies reported QoL post-surgery for RCC. Patients who underwent PN reported better scores, in many aspects of QoL [188]. Those who underwent RN reported more fear associated with living with only one kidney. Regardless of the intervention, patients with RCCs < 4 cm and a normal contralateral kidney showed the highest QoL scores after treatment, which matched their pre-diagnosis scores. Those with more complications had lower QoL scores [169].

No prospective comparative studies reporting oncological outcomes for minimally invasive ablative procedures compared with RN were identified. One trial reported on RFA vs. RN or PN for T1a RCC, resulting in CSS of 100% for all three treatments [194].

Patient and tumour characteristics permitting, the current oncological outcomes evidence base suggests that localised RCCs are best managed by PN rather than RN, irrespective of the surgical approach. Where open surgery is necessary, the oncological outcomes following open PN are at least as good as open RN and PN should be the preferred option when feasible.

Partial nephrectomy is unsuitable in some patients with localised RCC due to:
*   locally advanced tumour growth;
*   partial resection is not feasible due to unfavourable tumour location;
*   significant deterioration in patient health.

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 [195]. Multivariate analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at 5 or 10 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)
Lymph node dissection (LND) in RCC is controversial [196]. Clinical assessment of LNs status is based on enlargement of LNs on CT/MRI and intraoperative assessment by direct palpation. Less than 20% of clinically positive (cN+) LNs are confirmed to be metastatic at pathology (pN+) [197]. Computed tomography and MRI do not allow detection of small metastases in normal sized LN [198] and extended LND (e-LND) with histopathological examination is the only way to assess LN status. For clinically positive LNs (cN+) see Section 7.2. on locally advanced RCC.

In patients with clinically negative LN (cN0) six clinical trials have been reported [196], one RCT [197] and five comparative studies [199-203].

Retrospective series support the hypothesis that LND may be beneficial in high-risk patients [198, 204]. However, in the European Organization for Research and Treatment of Cancer (EORTC) study only 4% of cN0 patients had positive LNs at final pathology, suggesting that LND represents over-treatment in the majority of patients [197].

Retrospective studies suggest that eLND should involve the LNs surrounding the ipsilateral great vessel and the interaortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of interaortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases [198, 199, 205]. At least 15 LNs should be removed [206, 207]. Sentinel LND is an investigational technique [208, 209]. Better survival outcomes are seen in patients with a low number of positive LNs (< 4) and no extranodal extension [210, 211]. A pre-operative nomogram to predict pN+ LNs status has been proposed [212].

7.1.2.2.3 Embolisation
Before routine nephrectomy, tumour embolisation has no benefit [213, 214]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [215-217]. 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
Partial nephrectomy achieves similar oncological outcomes to radical nephrectomy for clinically localised tumours (cT1).	1b
Ipsilateral adrenalectomy, in the absence of clinical evident adrenal involvement during radical nephrectomy or partial nephrectomy, has no survival advantage.	3
In patients with localised disease without evidence of lymph node metastases, there is no survival advantage of lymph node dissection in conjunction with radical nephrectomy.	1b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	GR
Surgery is recommended to achieve cure in localised RCC.	B
Partial nephrectomy is recommended in patients with T1a tumours.	A
Favour partial nephrectomy over radical nephrectomy in patients with T1b tumour, whenever feasible.	B
Ipsilateral adrenalectomy is not recommended when there is no clinical evidence of invasion of the adrenal gland.	B
Lymph node dissection is not recommended in localised tumour without clinical evidence of lymph node invasion.	A

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 [218] and retrospective database reviews are available, mostly of low methodological quality [169, 219, 220]. Similar oncological outcomes for laparoscopic vs. open RN were found. Data from one RCT [221] and two NRSs [169, 218] showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic RN group compared with the open group. Convalescence time was also significantly shorter [218]. 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 [169, 218, 221]. Surgical complications were marked by low event rates and 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 [169].

Some comparative studies focused on the peri-operative outcomes of laparoscopic vs. RN for renal tumours ≥ T2. Overall, patients who underwent laparoscopic RN were shown to have lower estimated blood loss, less post-operative pain, shorter length of stay and convalescence compared to those who underwent open RN [218, 222-224]. Intraoperative and post-operative complications were similar in the two groups [218, 222-225]. No significant differences in CSS, PFS and OS were reported [207, 218, 223, 225, 226] (LE 2b).

The best approach for RN was the retroperitoneal or transperitoneal with similar oncological outcomes in the two RTCs [227, 228] and one quasi-randomised study [229]. Quality of life variables were similar in the two approaches.

Hand-assisted vs. standard laparoscopic RN was compared in one RCT [229] and one database review [191]. Estimated 5-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 [191, 229]. However, the sample size was small.

Robot-assisted laparoscopic RN vs. laparoscopic RN was compared in one small study [230]. 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 [231, 232]. Peri-operative outcomes were similar.

7.1.3.2 *Partial nephrectomy techniques*

Studies comparing laparoscopic PN and open PN found no difference in PFS [233-236] and OS [235, 236] in centres with laparoscopic expertise. The mean estimated blood loss is lower with the laparoscopic approach [233, 235, 237], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events are similar [233, 235]. Operative time is generally longer with the laparoscopic approach [234-236] and warm ischaemia time is shorter with the open approach [233, 235, 237, 238]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [236], but not after a follow-up of 3.6 years. In another comparative study, the surgical approach was not an independent predictor for post-operative chronic kidney disease [238]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [239]. Simple tumour enucleation has similar PFS and CSS rates compared to standard PN and RN in a large study [240, 241].

The feasibility of off-clamp laparoscopic PN and laparoendoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm their safety and clinical role [242, 243].

No studies have compared the oncological outcomes of robot-assisted vs. laparoscopic or open PN. 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 ischemia time, operative time, immediate, early, and short-term complications, variation of creatinine levels, and pathologic margins were similar among the groups [12].

A recent meta-analysis including a series of NRS 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 ischemia time, smaller change of 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 [13].

7.1.3.3   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

Recommendations	GR
Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localised masses not treatable by partial nephrectomy.	B
Radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.	B

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 for patients treated with surgery [244, 245]. 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 [244]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [11, 246, 247].

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 [248, 249]. 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 [250].

In the largest reported series of active surveillance, the growth of renal tumours was low and progression to metastatic disease was reported in a limited number of patients [251, 252].

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 multivariable analysis, management type was not associated with OS after adjusting for age, comorbidity, and other variables [248]. No statistically significant difference in OS and CSS were observed in another study of RN vs. PN vs. active surveillance for T1a renal masses with a follow-up of 34 months [253].

The initial results of the multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry were recently published. This prospective, non-randomised study prospectively enrolled 497 patients with solid renal masses < 4 cm in size who chose active surveillance or primary active intervention. Patients who chose active surveillance were older, had worse ECOG scores, more comorbidities, smaller tumours, and more often multiple and bilateral lesions. Overall survival for primary intervention and active surveillance was 98% and 96% at 2 years, and 92% and 75% at 5 years, respectively (p = 0.06). At 5 years CSS was 99% and 100%, respectively (p = 0.3). Active surveillance was not predictive of overall or CSS in regression modelling with relatively short follow-up [19].

Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, active surveillance is appropriate to initially monitor small renal masses, followed if required, by treatment for progression [250-252, 254-257].

A multicentre study assessed patient QoL undergoing immediate intervention vs. active surveillance. Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least 1 year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on active surveillance [258].

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 [259-261]. One comparative study reported similar OS, CSS, and RFS in 172

laparoscopic patients with a longer follow-up compared with 123 percutaneous patients with a shorter follow-up [260]. A shorter average length of hospital stay was found with the percutaneous technique [260, 261]. No studies compared surveillance strategies to cryoablation.

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, disease-free survival (DFS), local recurrence or progression to metastatic disease [262, 263], and some showing significant benefit for the PN techniques for some or all of these outcomes [264-267]. Not all studies reported all outcomes listed, and some were small and included benign tumours. No study showed oncological benefit for the cryoablation technique over PN.

Peri-operative outcomes, complication rates and other quality of life measures were also mixed. Some studies found the length of hospital stay was shorter and surgical blood loss was less with cryoablation [262-264], while also finding no differences in other peri-operative outcomes, recovery times, complication rates or post-operative serum creatinine levels. Two studies [266, 267] 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 the two studies, but in favour of cryoablation in a third [265-267]. Estimates of new CKD were also mixed, with one study in favour of cryoablation [265], another strongly in favour of PN [266], and the third showing no difference [267]. One study compared PN with ablation therapy, either cryoablation or RFA [268], and showed significantly improved disease-specific survival at both 5 and 10 years for PN.

7.1.4.3.3   Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Three studies compared patients with T1a tumours treated by laparoscopic or percutaneous RFA [269-271]. 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 [271] 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 [194, 272, 273].

One study [272] 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. CSS was 100% in both groups. OS was lower in the RFA group but patients treated with surgery were younger [194].

In a monocentric study that compared 34 RFA patients to 16 open PN patients, there was a higher rate of complications and transfusions in the PN group. Although the tumours were larger in PN patients, progression rates were similar (0%) [273].

7.1.4.3.5   Cryoablation versus radiofrequency ablation

Two studies compared RFA and cryoablation [274, 275]. No significant differences were reported for OS, CSS, or RFS in either study. For local RFS at 5 years, one study [274] reported improvement with RFA, while the other [275] reported a benefit with cryoablation. One study [274] 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 recommendations

Summary of evidence	LE
Population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management. However, the same benefit in cancer-specific mortality is not confirmed in analyses focusing on older patients (> 75 years).	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 minimally invasive therapies compared to partial nephrectomy.	3

Recommendations	GR
Due to the low quality of available data no recommendation can be made on radiofrequency ablation and cryoablation.	C
In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, radiofrequency ablation and cryoablation may be offered.	C

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 of 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 [36]. However, the extent of LND is controversial [198].

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 [215-217]. The use of neoadjuvant targeted therapy to downsize tumours is experimental and cannot be recommended outside controlled clinical trials.

7.2.4   Management of RCC with venous thrombus
Tumour thrombus formation in the IVC in RCC patients is a significant adverse prognostic factor. Traditionally, patients with VTT undergo surgery to remove the kidney and tumour thrombus (TT). Aggressive surgical resection is widely accepted as the default management option for patients with VTT [276-284]. 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 VTT
The data on whether patients with VTT should undergo surgery is derived from case series. In one of the largest published studies [281] 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 VTT, and an acceptable performance status (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 TT (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 VTT in non-metastatic RCC [5, 285]. Only 5 studies were eligible for final inclusion. There were high risks of bias across all studies.
        Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [286, 287]. Pre-operative embolisation [288] 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 [289].
        No surgical method was shown to be superior for the excision of VTT. The surgical method was dependent on the level of TT, and the grade of occlusion of the IVC [5, 286, 287, 289]. 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

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	GR
In patients with clinically enlarged lymph nodes, lymph node dissection may be performed for staging purposes or local control.	C
Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic RCC.	C

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 [290-294] (LE: 1b). Heat shock protein-peptide complex-96 (vitespen) [23], 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) [295]. 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 of adjuvant sunitinib, sorafenib, pazopanib, axitinib and everolimus are ongoing. At present, there is no evidence for the use of adjuvant VEGF-R or mammalian target of rapamycin inhibitor (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% information. 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 [144].

7.2.5.1   Summary of evidence and recommendation for adjuvant therapy

Summary of evidence	LE
Adjuvant cytokines do not improve survival after nephrectomy.	1b
Adjuvant sunitinib or sorafenib do not improve disease-free and overall survival after nephrectomy.	1b

Recommendations	GR
Adjuvant therapy with sunitinib or sorafenib should not be given.	A
Do not provide adjuvant therapy following surgery outside of controlled clinical trials.	A

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 [296]. 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 good PS, large primary tumours and low metastatic volume. In patients with poor PS or Metastatic Renal Cancer Database Consortium (IMDC) risk, those with 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 [215-217] (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

Recommendations	GR
Cytoreductive nephrectomy is recommended in appropriately selected patients with metastatic RCC.	C

7.3.2   *Local therapy of metastases in mRCC*
A SR of the local treatment of metastases from RCC in any organ was undertaken [297]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes were OS, CSS and PFS, local symptom control and adverse events. A risk-of-bias assessment was conducted [298]. Of 2,235 studies identified only 16 non-randomised comparative studies were included.

Eight studies reported on local therapies of RCC-metastases in various organs [299-306]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [307-309], two in the brain [310, 311] and one each in the liver [312] lung [313] and pancreas [314]. Three studies [303, 305, 313] were abstracts. Data were too heterogeneous for a 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 [299-306] on RCC metastases in various organs compared complete vs. no and/or incomplete metastasectomy. However, in one study [302], 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 [299, 301-303, 305, 306] reported a significantly longer median OS or CSS following complete metastasectomy (the median value for median OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for median OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one [300] showed no significant difference in CSS between complete and no metastasectomy, and one [304] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases to the lung [313], liver [312], and pancreas [314], 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 5-year OS for metastasectomy vs. no metastasectomy.

7.3.2.2   *Local therapies for RCC bone metastases*
Of three studies identified, one [309] compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases. Single-dose IGRT (≥ 24 Gray) had a significantly better 3-year actuarial local PFS rate, also shown by Cox regression analysis. Another study [307] compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations. A significantly higher 5-year CSS rate was observed in the intervention group.

After adjusting for prior nephrectomy, gender and age, multivariate analysis still favoured metastasectomy/curettage and stabilisation. A third study [308] 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. 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 [310] 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 2-year OS and intracerebral control for SRS + WBRT based on only three participants. The other study [311] compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy (MTS) + CRT or CRT alone. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. 1-, 2- and 3-year survival rates were higher but not significantly so for FSRT than for metastasectomy + CRT or CRT alone. Fractionated stereotactic radiotherapy did not result in a significantly better 2-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 [315]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [316] (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	GR
No general recommendations can be made. The decision to resect metastases has to be taken for each site, and on a case-by-case basis; performance status, risk profiles, patient preference and alternative techniques to achieve local control such as stereotactic radiotherapy, must be considered.	C
Stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases may be offered for local control and symptom relief.	C

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 [317]. However, in one study, interferon-alpha (IFN-α) showed equivalent efficacy to IFN-α + interleukin-2 (IL-2) + 5-FU [318].

7.4.1.1 Summary of evidence and recommendation for systemic therapy for advanced/metastatic RCC

Summary of evidence	LE
In metastatic RCC, 5-FU combined with immunotherapy has equivalent efficacy to IFN-α.	1b
In metastatic RCC, chemotherapy is otherwise not effective.	3

Recommendation	GR
In patients with clear-cell metastatic RCC, chemotherapy should not be offered.	B

5-FU = fluorouracil; INF = interferon.

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 [319]. IFN-α resulted in a response rate of 6-15%, a 25% decrease in tumour progression risk and a modest survival benefit compared to placebo [87, 320]. However,

patients with intermediate-risk disease, failed to confirm this benefit [321].

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 [319]. The moderate efficacy of immunotherapy was confirmed in a Cochrane meta-analysis [320]. Bevacizumab + IFN-α increased response rates and PFS in first-line therapy compared with IFN-α monotherapy [322]. All studies comparing targeted drugs to IFN-α monotherapy therapy showed superiority for sunitinib, bevacizumab + IFN-α, and temsirolimus [322-325]. IFN-α has been superseded by targeted therapy in cc-mRCC.

Table 7.1: MSKCC (Motzer) criteria [87]*

Risk factors**	Cut-off point used
Karnofsky PS	< 80
Time from diagnosis to treatment	< 12 months
Haemoglobin	< Lower limit of laboratory reference range
LDH	> 1.5 times the upper limit of laboratory range
Corrected serum calcium	> 10.0 mg/dL (2.4 mmol/L)

The Metastatic Renal Cancer Database Consortium (IMDC) risk model is also widely used in this setting [326].
** *Favourable (low) risk, no risk factors; intermediate risk, one or two risk factors; poor (high) risk, three or more risk factors.*
LDH = lactate dehydrogenase; PS = performance status.

7.4.2.2 Interleukin-2
Interleukin-2 has been used to treat mRCC since 1985, with response rates ranging from 7% to 27% [325, 327, 328]. Complete and durable responses have been achieved with high-dose bolus IL-2 [329]. The toxicity of IL-2 is substantially greater than that of IFN-α [320].

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 [330]. 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 [331], 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 Programmed Death-1 (PD-1) or the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)-signalling to restore tumour specific T cell immunity [332]. While pembrolizumab and nivolumab target the PD-1 receptor, atezolizumab and durvalumab block the ligand, PD-L1. Ipilumimab targets CTLA-4. A randomised dose ranging phase II trial of nivolumab in metastatic RCC patients revealed a high ORR with rapid and durable responses in heavily pre-treated patients [333]. A phase III trial is currently investigating the combination of nivolumab and ipilumimab vs. sunitinib in first line treatment (CheckMate 214, NCT 02231749) [148]). A phase III trial of nivolumab vs. everolimus after several lines of VEGF-targeted therapy (CheckMate 025, NCT01668784) reported longer OS, better QoL and fewer grade 3 or 4 adverse events with nivolumab than with everolimus [153, 334, 335]. Nivolumab has superior OS to everolimus (Hazard Ratio [HR]: 0.73, 95% CI: 0.57-0.93, p < 0.002) in VEGF refractory renal cancer 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.

7.4.2.5 Summary of evidence and recommendations for immunotherapy in mRCC

Summary of evidence	LE
IFN-α monotherapy is inferior to VEGF-targeted therapy or mTOR inhibition in metastatic RCC.	1b
IL-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.	2-3
High dose 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 tumours.	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	GR
Nivolumab is strongly recommended after one or two lines of VEGF-targeted therapy in metastatic RCC.	A
Monotherapy with IFN-α or HD bolus IL-2 is not routinely recommended as first-line therapy in metastatic RCC.	A

HD = high-dose; IL = interleukin; INF = interferon; OS = overall survival; PFS = progression-free survival; PS = performance status; VEGF = vascular endothelial growth factor.

7.4.3 *Targeted therapies*

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL inactivation results in overexpression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [336-338]. 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:
- sorafenib (Nexavar®);
- sunitinib (Sutent®);
- bevacizumab (Avastin®) combined with IFN-α;
- pazopanib (Votrient®);
- temsirolimus (Torisel®);
- everolimus (Afinitor®);
- axitinib (Inlyta®).

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 [319] (Table 7.1). Since the MSKCC (Motzer) criteria were developed during the cytokine era, the IMDC risk model has been established and validated to yield an accurate prognosis for 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 [326].

The IMDC published data on conditional survival which may be used in patient counselling [339]. 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 [340].

Table 7.2: Median OS and patients surviving 2 years treated in the era of targeted therapy per IMDC risk group (based on references [326, 340]**)**

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 [340]; ** based on [326]*
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 multikinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS [341] (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 [342]. 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 [343]). First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN-α. Overall survival was greater in patients treated for 26.4 and 21.8 months with sunitinib despite crossover [344].

In the EFFECT trial, sunitinib 50 mg/day (4 weeks on/2 weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with clear-cell mRCC [345]. 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 (2 weeks on/1 week off) is being used to manage toxicity, but robust data to support its use is lacking.

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 [346]. 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-pretreated 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 [347], 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 [348]. 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) [349].

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%. OS 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 [350, 351].

Axitinib was investigated in two first-line studies [352, 353]. One investigated the efficacy and safety of axitinib dose titration in previously untreated patients with mRCC. Although the objective response rate (RR) was higher in patients treated to toxicity, median PFS was 14.5 months in the axitinib titration group, 15.7 months in the placebo titration group, and 16.6 months in non-randomised patients [352]. This supports the hypothesis that dose escalation is associated with higher RRs.

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 [353]. 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 tyrosine kinases, 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 [152]. Based on these results a randomised phase III trial investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapy (METEOR) [56]. Cabozantinib delayed PFS compared to everolimus in VEGF targeted therapy refractory disease by 42% (HR: 0.58 95% CI: 0.45-0.75) [56] (LE: 1b). The median PFS for cabozantinib was 7.4 (95% CI: 5.6-9.1) months vs. 3.8 (95% CI: 3.7-5.4) months for everolimus. The trial recruited 658 patients although PFS was assessed on the first 375 patients. Interim OS results show a strong trend favouring cabozantinib (HR: 0.67: 95% CI: 0.51-0.89, p = 0.005), however this was not significant at the predefined levels at this interim stage. A final planned mature OS analysis is expected in 2016. Grade 3 or 4 adverse events in 74% were reported 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 2 drugs. The trial included 16% MSKCC poor-risk patients.

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 AVOREN study compared bevacizumab + IFN-α with INF-α monotherapy in mRCC [322]. 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) [354].

A similarly designed trial (CALGB 90206) [355, 356], of bevacizumab + IFN-α vs. Interferon-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 [357]. Patients with modified high-risk mRCC in the NCT00065468 trial received first-line temsirolimus or IFN-α monotherapy, or a combination of both [324]. Median OS was higher in the temsirolimus group. However, OS in the temsirolimus + IFN-α group was not significantly superior to IFN-α alone [324]. IFN-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 [358]. Based on these results, temsirolimus is not recommended in patients with VEFG 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) [359]. The initial data showed a median PFS of 4.0 months v.s. 1.9 months for everolimus and placebo, respectively [359]. This was extended to 4.9 months in the final analysis (HR: 0.33) [360]. Subset analysis of PFS for patients receiving only 1 previous VEFG TKI was 5.4 months [361]. This included some patients who were intolerant rather than progressed on therapy (PFS was also 5.4 months) [362]. RECORD-1 included patients who failed multiple lines of VEGF-targeted therapy, and received everolimus in a third- and fourth-line setting [359].

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 [363]. 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 and recommendations***
7.4.6.1   *Therapy for treatment-naïve patients with clear-cell mRCC*
Key trials have established sunitinib 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 COMPARZ study demonstrated that pazopanib and sunitinib have similar efficacy and different toxicity profiles. This study firmly establishes pazopanib as another first-line option [347].

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 until disease progression followed by everolimus as one of the treatment options for patients with mRCC [359]. However, both nivolumab and cabozantinib were superior to everolimus following a similar trial design as RECORD-1 [153]. 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 a superior PFS compared to everolimus. Cabozantinib's trend toward an OS advantage at interim analysis (HR: 0.67: 95% CI: 0.51-0.89, p = 0.005), further supports its use in this setting. If this becomes statistically significant in the final analysis the recommendations will match those of nivolumab.

Axitinib is superior to sorafenib in terms of PFS in sunitinib refractory ccRCC [348]. Neither nivolumab nor cabozantinib has been tested directly against axitinib in the second-line setting. However, the OS advantage and tolerability of nivolumab over everolimus in this setting makes it preferable to axitinib, while the impressive PFS of cabozantinib, especially in those who have failed sunitinib, makes it an attractive alternative to axitinib.

Tolerability is an important consideration when recommendations cannot be made of 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 [349-351, 359].

INTORSECT compared temsirolimus vs. sorafenib after disease progression on sunitinib [358]. 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 OS difference, 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-targeted therapy-refractory RCC (LE: 1a). There is a strong rationale for using both drugs in sequence in the 2nd and 3rd line following VEGF-targeted therapy. This creates a new a standard for the majority of patients. Nivolumab was approved in this setting in the United States in 2015. It remains unclear about when these drugs will be approved elsewhere.

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 (expert opinion and [364]).

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 [349-351].

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
The RECORD-1 study demonstrated the activity of everolimus in patients who had received more than one line of targeted therapy. Twenty six percent of patients were treated with two or more lines of VEGF-targeted

therapy and significant benefits were seen. However, based on the results of the influential nivolumab and cabozantinib trials, a strong rationale exists for preferring both drugs as third-line treatment upon failure of 2 VEGF-targeted therapies [56, 153] (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 [364]). This sequence is not recommended where alternative superior drugs are available.

7.4.6.1.1.5 Combination of targeted agents
There have been a number of trials with VEFG targeted therapy and mTOR inhibitors [365-369]. The results have all been negative. No combinations of targeted agents are currently recommended.

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 [324, 370-372].

The most common non-clear-cell subtypes are papillary type 1 and non-type 1 pRCCs. There are small single-arm data for sunitinib and everolimus [372-375]. A trial of both types of pRCC treated with everolimus (RAPTOR) [375], showed 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 foretenib (a dual MET/VEGFR2 inhibitor) in patients with pRCC. Toxicity was acceptable with a high RR in patients with germline MET mutations [376]. However, a randomised phase II trial of everolimus vs. sunitinib (ESPN) with crossover design in non-clear-cell mRCC included 73 patients (27 with pRCC) and was stopped after a futility analysis for PFS and OS [377]. 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 [126, 378]. Patients with ncc-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 [324, 370].

Figure 7.1: Recommendations for patients with metastatic ccRCC who have failed one or more lines of VEGF targeted therapy

Recommend with OS advantage

Recommend without OS

Recommend if other options not available

| First line | Second line | Third line | Fourth line |

sunitinib pazopanib

nivolumab

cabozantinib

cabozantinib

nivolumab

axitinib

everolimus-axitinib

everolimus

4th line therapy should focus on drugs not previously given, especially nivolumab or cabozantinib
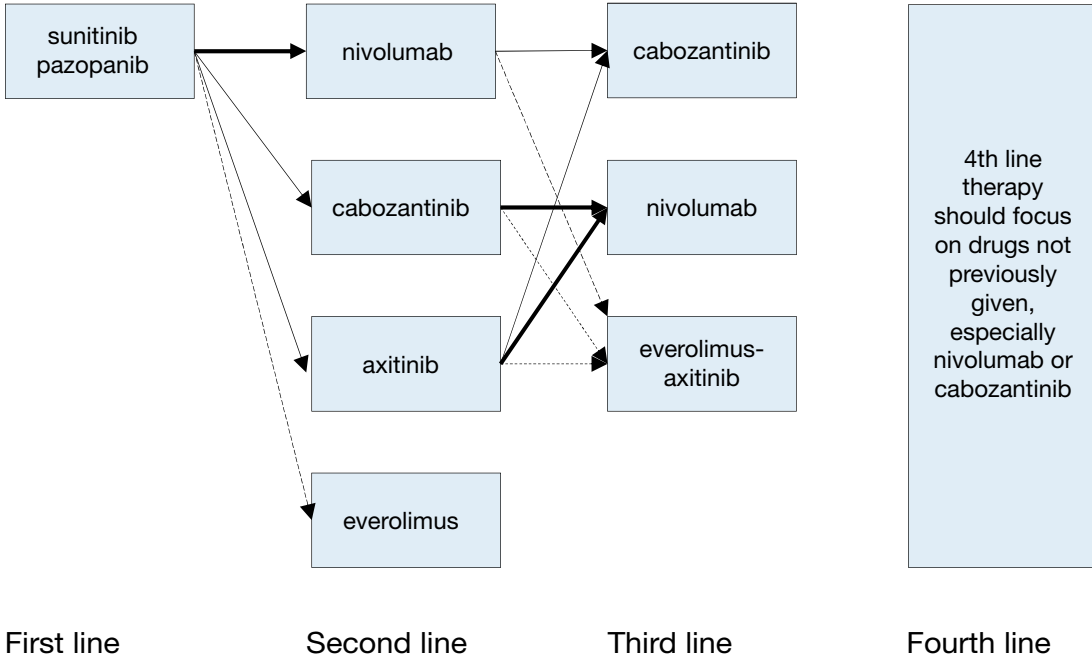
Table 7.3: EAU 2015 evidence-based recommendations for systemic therapy in patients with mRCC

RCC type	MSKCC risk group [319]	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 based on PFS: cabozantinib axitinib sorafenib# everolimus&	2a 2a 2a 2a 2a	after VEGF therapy: nivolumab cabozantinib everolimus& after VEGF and mTOR therapy: sorafenib after VEGF and nivolumab: cabozantinib axitinib everolimus	2a 2a 2a 1b 4 4 4	any targeted agent	4
Clear cell*	poor¶	temsirolimus	1b	any targeted agent	4				
Non-clear cell §	any	sunitinib everolimus temsirolimus	2a 2b 2b	Any targeted agent	4				

IFN-α = interferon alpha; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin inhibitor; RCC = renal cell carcinoma; TKI= tyrosine kinase inhibitor.

* Doses: IFN-α - 9 MU three times per week subcutaneously, bevacizumab 10 mg/kg biweekly intravenously; sunitinib 50 mg daily orally for 4 weeks, followed by 2 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.

§ 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.

¶ Poor risk criteria in the NCT00065468 trial consisted of MSKCC [319] risk plus metastases in multiple organs. Evidence for subsequent therapies unclear, making this option less appealing.

 # Sorafenib was inferior to axitinib in a RCT in terms of PFS but not OS [351].

^ Level of evidence was downgraded in instances when data were obtained from subgroup analysis within an RCT.

& 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.

7.4.6.3 Summary of evidence and recommendations for systemic therapy in mRCC

Summary of evidence	LE
VEGF 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
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 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.	1b
Sorafenib has broad activity in a spectrum of settings in clear-cell renal cancer 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 VEFG-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.	1a

Recommendations	GR
Systemic therapy for mRCC should be based on targeted and immune agents.	A
Sunitinib and pazopanib are recommended as first-line therapy for advanced/metastatic ccRCC.	A
Bevacizumab + IFN-α are recommended as first-line therapy for advanced/metastatic RCC in favourable-risk and intermediate-risk ccRCC.	A
Temsirolimus is recommended as first-line treatment in poor-risk RCC patients. Data on subsequent therapies is lacking in this setting.	A
Cabozantinib should be given for ccRCC patients who progressed after one or two lines of VEGF-targeted therapy based on a PFS advantage over everolimus.	A
Nivolumab is strongly recommended for ccRCC patients who progressed after one or two lines of VEGF-targeted therapy based on an OS advantage over everolimus.	A
Axitinib can be given as second-line treatment for mRCC after cytokines or first-line VEGF where other drugs are not safe, tolerable or available.	A
Everolimus can be given for ccRCC patients who failed VEGF-targeted therapy where other drugs are not safe, tolerable or available.	A
Sequencing of targeted agents is strongly recommended.	A
Sunitinib or everolimus can be given as first-line therapy for non-clear cell mRCC.	B

ccRCC = clear-cell renal cell carcinoma; INF = interferon alpha; PFS = progression-free survival;
mRCC = metastatic renal cell carcinoma; VEGF = vascular endothelial growth factor.

7.5 Recurrent RCC
7.5.1 Introduction
Locally recurrent disease can occur after RN, PN and thermal ablation. After nephron sparing treatment approaches 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 rates for pT1 tumours after PN are observed in 2.2% and are generally managed surgically depending on the extent of the loco-regional recurrence [379]. After thermal ablation loco-regional recurrences (intrarenal and regional) have been described in up to 12% [380]. 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 not 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 (Section 7.3). Isolated local recurrence however is rare.

The largest series on the treatment of isolated recurrence was published in 2009 [381]. Of 2,945 patients who underwent nephrectomy the authors identified 54 isolated local recurrences in the renal fossa. These however included those 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 [381]. 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	GR
Surgical resection of local recurrent disease may be offered.	C

8.   FOLLOW-UP AFTER RADICAL NEPHRECTOMY OR PARTIAL NEPHRECTOMY OR ABLATIVE THERAPIES FOR 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 the urologist, who should record the time to recurrence or the development of metastases. 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 [382, 383] and non-cancer survival [173-175] can be optimised by performing NSS whenever possible for T1 and T2 tumours [384] (LE: 3). Recurrence after PN is rare, but early diagnosis is useful, as the most effective treatment is redux surgery [385, 386]. Recurrence in the contralateral kidney is also rare and might be related to positive margins, multifocality, and grade [387] (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, 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 [33, 388, 389] (LE: 4):

- The sensitivity of chest radiography and US for small metastases is poor.

Surveillance with these imaging modalities should be done with the acknowledgement of these limitations [390]. With low-risk tumours, surveillance intervals should be adapted taking into account radiation exposure and benefit. To reduce radiation exposure, MRI can be used.

- When the risk of relapse is intermediate or high, CT of the chest and abdomen should be performed, although significant morbidity associated with the radiation exposure involved in repeated CT scans should be taken into account [391].
- Surveillance should also include evaluation of renal function and cardiovascular risk factors.
- Positron-emission tomography (PET) and PET-CT as well as bone scintigraphy should not be used in RCC surveillance, due to limited specificity and sensitivity.

There is controversy over 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 [182] (LE: 3).

Several authors [158, 160, 392, 393], 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 [394] (LE: 2). Using prognostic variables, several stage-based surveillance regimens have been proposed [395, 396], but do not include ablative therapies. A post-operative nomogram is available for estimating the likelihood of freedom from recurrence at 5 years [155]. Recently, a pre-operative prognostic model based on age, symptoms, and TNM staging has been published and validated [164] (LE: 3). A surveillance algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient 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.

Table 8.1: Proposed surveillance schedule following treatment for RCC, taking into account patient risk profile and treatment efficacy

Risk profile	Treatment	Surveillance						
		6 mo	1 y	2 y	3 y	4 y	5 y	> 5 y
Low	RN/PN only	US	CT	US	CT	US	CT	Discharge
Intermediate	RN/PN/ cryo/ RFA	CT	CT	CT	US	CT	CT	CT once every 2 years
High	RN/PN/ cryo/ RFA	CT	CT	CT	CT	CT	CT	CT once every 2 years

Cryo = cryotherapy; CT = computed tomography of chest and abdomen, or MRI = magnetic resonance imaging; PN = partial nephrectomy; RFA = radiofrequency ablation; RN = radical nephrectomy; 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

Recommendations	GR
Follow-up after RCC should be based on the risk of recurrence.	C
For low-risk disease, CT/MRI can be used infrequently.	C
In intermediate-risk patients, intensified follow-up should be performed, including CT/MRI scans at regular intervals in accordance with a risk-stratified nomogram.	C
In high-risk patients, the follow-up examinations should include routine CT/MRI scans.	C
Follow-up should be intensified in patients after NSS for tumours > 7 cm or with a positive surgical margin.	C
Risk stratification can be based on pre-existing classification systems such as the UISS integrated risk assessment score (http://urology.ucla.edu/body.cfm?id=443).	C

CT = computed tomography; MRI = magnetic resonance imaging; NSS = nephron-sparing surgery;
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.

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10.   CONFLICT OF INTEREST

EAU Guidelines on
Testicular Cancer

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**European
Association
of Urology**

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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.

1.2 Panel composition

The EAU Guidelines Panel on Testicular Cancer consists of a multidisciplinary group of clinicians including, urologists, a pathologist, oncologists and radiotherapists. Members of this panel have been selected, based on their expertise, to represent the professionals treating patients suspected of harbouring 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, the 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 2015 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 2016 Testicular Cancer Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. For this 2016 print, updates include:
- A new flowchart (Figure 2) on Treatment options in patients with seminoma clinical state IIA and IIB.
- A new section on Quality of life and long-term toxicities after cure for testicular cancer (Section 8.6).

Conclusions and recommendations have been rephrased and added to throughout the current document. Changed or new conclusions and recommendations can be found in sections:

5.9 Guideline for the Diagnosis and staging of testicular cancer

Recommendation	GR
Offer biopsy of the contralateral testis and discuss its consequences with patients at high risk for contralateral TIN.	A

TIN = testicular intraepithelial neoplasia.

7.2.2 Guideline for the treatment of stage I seminoma

Recommendation	GR
If carboplatin-based adjuvant chemotherapy is considered, offer one course at AUC 7	A

AUC = area under curve.

7.5.6   Guideline for the treatment of metastatic germ cell tumours

Recommendation	LE	GR
In seminoma stage CS IIA/B, offer chemotherapy (3 x BEP or 4 x EP, in good prognosis) as an alternative to radiotherapy.	1	A

EP = etoposide, cisplatin; BEP = cisplatin, etoposide, and bleomycin.

7.3.6   Guidelines for the treatment of NSGCT stage I

CS1B (pT2-pT4): high risk	LE	GR
Recommend primary chemotherapy with one course of BEP.	2a	A*
Inform patients about the advantages and disadvantages of two courses of BEP.	2a	A*

BEP = cisplatin, etoposide, and bleomycin.

* Upgraded following panel consensus

Table 8.1: Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma

Procedure	Year			
	1	2	3	4-5
Physical examination	4 times	4 times	4 times	Once/year
Tumour markers	4 times	4 times	4 times	Once/year
Plain radiography chest	Twice	Twice	Twice	Twice
Abdominopelvic CT	Twice at 3 and 12 months	Once at 24 months	Once at 36 months	

CT = computed tomography.

Table 8.2: Recommended minimum follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma

Procedure	Year				
	1	2	3	4-5	6-10
Physical examination	4 times	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice	Twice		
Abdominopelvic CT	Once	Once	Once	Once/year	

CT = computed tomography.

Table 8.3: Recommended minimum follow-up schedule for post-orchiectomy surveillance, radiotherapy or chemotherapy: stage I seminoma

Procedure	Year		
	1	2	3-5
Physical examination	3 times	3 times	Once/year
Tumour markers	3 times	3 times	Once/year
Plain radiography chest	Twice	Twice	
Abdominopelvic CT	Twice	Twice	at 36 and 60 months

CT = computed tomography.

Table 8.4: Recommended minimum follow-up schedule in metastatic NSGCT and seminoma

Procedure	Year			
	1	2	3-5	Thereafter
Physical examination	4 times	4 times	Twice/year	Once/year
Tumour markers	4 times	4 times	Twice/year	Once/year
Plain radiography chest	4 times	4 times	Twice/year	Once/year
Abdominopelvic CT*†	Twice	Twice	Once/year	As indicated
Chest CT†‡	Once/year	Once/year	Once/year	As indicated
Brain CT§	Once/year	Once/year	Once/year	As indicated

CT = computed tomography.

* An abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.

† If the post-chemotherapy evaluation in a seminoma patient shows any mass > 3 cm, the appropriate CT should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET/CT can be performed.

‡ A chest CT is indicated if abnormality is detected on a plain radiography chest and after pulmonary resection.

§ In patients with headaches, focal neurological findings, or any central nervous system symptoms.

2. METHODS

For the Germ-cell tumour Section, the literature has been assessed and updated throughout the document. For the Testicular Stromal tumours a scoping search as of Jan 1st, 2009 until October 13th, 2014 has been carried out. No restrictions on data level were applied. The search identified 758 unique records, of which 18 references were included in the manuscript.

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. 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.

2.2 Future goals

The results of ongoing and new systematic reviews will be included in the 2017 update of the Testicular Cancer Guidelines. These reviews are performed using standard Cochrane systematic review methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Ongoing systematic review:
• Risk factors for relapse in Seminoma Stage I in Active Surveillance.

Topics selected for subsequent systematic reviews:
• What is the cure rate of patients with germ cell tumours undergoing salvage chemotherapy (including high-dose)?
• What is the rate of long-term toxicities (>10 yrs) after chemotherapy and radiotherapy of metastatic germ cell tumours?

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 society [3, 4]. Its incidence has been increasing during the last decades especially in industrialised countries [5, 6]. 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 [7].

At diagnosis, 1-2% of cases are bilateral and the predominant histology is germ cell tumour (90-95% of cases) [3]. 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 [8], 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 [9, 10]. 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) [11]. In the same context, the frequency of post-chemotherapy residual tumour resection is associated with perioperative mortality and OS [12, 13].

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 [14] and in testicular intraepithelial neoplasia (TIN). Alterations in the p53 locus have been identified in 66% of cases of testicular TIN [15]. 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 TIN and germ cell neoplasia. 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 [16, 17].

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) [18, 19], familial history of testicular tumours among first-grade relatives and the presence of a contralateral tumour or TIN [14, 18, 20-22]. Very tall men seem to have a higher risk of GCT (OR 3.35), while short stature is protective [23, 24], although further confirmation is needed.

3.2 Pathological classification

The recommended pathological classification (modified from the 2004 version of the World Health Organization [WHO] guidance) is shown below [25]. In 2016, an update of the WHO pathological classification was published. The findings of this classification will be published in the 2017 update of the Testicular Cancer Guidelines.

1. **Germ cell tumours**
   - Intratubular germ cell neoplasia (IGCNU), unclassified type
   - Seminoma (including cases with syncytiotrophoblastic cells)
   - Spermatocytic seminoma (mention if there is a sarcomatous component)
   - Embryonal carcinoma
   - Yolk sac tumour
   - Choriocarcinoma
   - Teratoma (mature, immature, with malignant component)
   - Tumours with more than one histological type (specify percentage of individual components).
2. **Sex cord/gonadal stromal tumours**
   - Leydig cell tumour
   - Malignant Leydig cell tumour
   - Sertoli cell tumour
     - lipid-rich variant
     - sclerosing
     - large cell calcifying
   - Malignant Sertoli cell tumour

- Granulosa cell tumour
  - adult type
  - juvenile type
- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours
  - incompletely differentiated
  - mixed
- Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma).

3. **Miscellaneous non-specific stromal tumours**
- Ovarian epithelial tumours
- Tumours of the collecting ducts and rete testis
- Tumours (benign and malignant) of non-specific stroma.

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-orchiectomy 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-orchiectomy half-life kinetics
The mean serum half-life of AFP and hCG is 5-7 days and 2-3 days, respectively [26]. Tumour markers need to be re-evaluated after orchiectomy to determine half-life kinetics. Marker decline in patients with clinical stage 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 [27]. The persistence of elevated serum tumour markers after orchiectomy might indicate the presence of metastatic disease (macro- or microscopically), while the normalisation of marker levels after orchiectomy does not rule out the presence of tumour metastases. During chemotherapy, the markers should decline; persistence has an adverse prognostic value [28, 29]. Slow marker decline in patients with poor prognosis during the first cycle of standard BEP chemotherapy can be used as an indication for early chemotherapy dose intensification [30].

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.

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 [31]. Those figures decrease slightly in stages I and II [32, 33], with a rate of understaging of 25-30% [34]. New generations of CT devices do not seem to improve the sensitivity.

Magnetic resonance imaging (MRI) produces similar results to CT in the detection of retroperitoneal nodal enlargement [35, 36]. 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 [35], when CT is contraindicated because of allergy to contrast media, 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 has to be

recommended in all patients with TC as up to 10% of cases can present with small subpleural nodes that are not visible radiologically [37]. A CT has high sensitivity, but low specificity [35].

There is no evidence to support the use of fluorodeoxyglucose-PET (FDG-PET) in the staging of testis cancer [38, 39]. It is recommended in the follow-up of patients with seminoma with any residual mass at least 6 weeks after the end of the last cycle of chemotherapy in order to decide on watchful waiting or active treatment [40, 41]. Fluorodeoxyglucose-PET is not recommended in the re-staging of patients with NSGCT after chemotherapy [42, 43].

Other examinations, such as brain or spinal CT, bone scan or liver ultrasound, should be performed if there is suspicion of metastases to these organs. A CT or MRI of the skull 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

For staging purposes recommendations are:		
Test	**Recommendation**	**GR**
Serum tumour markers	AFP hCG LDH	A
Abdominopelvic CT	All patients	A
Chest CT	All patients	A
Testis ultrasound (bilateral)	All patients	A
Bone scan or 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 LH FSH Semen analysis		B
Discuss sperm banking with all men prior to to starting treatment for testicular cancer.		A

hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; CT = computed tomography;
LH = luteinising hormone; FSH = follicle-stimulating hormone ; AFP = alpha fetoprotein.

4.4 Staging and prognostic classifications

The staging system recommended in these guidelines is the 2009 TNM of the International Union Against Cancer (UICC) (Table 4.2) [44]. 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, 2009, 7th edn. [44])

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 (testicular intraepithelial neoplasia)
	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		**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 or 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
		M1b Other sites
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	S1 < 1.5 x N and	< 5,000 and	< 1,000
S2	S2 1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	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.
[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, SX
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any patientTX	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 IIC	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-orchiectomy serum tumour marker levels within normal limits. Marker decline in patients with clinical stage 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 orchiectomy, 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 [45, 46]. True stage IS (persistently elevated or increasing serum marker levels after orchiectomy) 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) [27].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group [47])*

Good-prognosis group	
Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	*All of the following criteria:* • Testis/retroperitoneal 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

Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate prognosis group	
Non-seminoma (28% of cases) 5-year PFS 75% 5-year survival 80%	*All of the following criteria:* • Testis/retroperitoneal 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
Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	*Any of the following criteria:* • 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
Seminoma	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 presents as a painless, unilateral testicular scrotal mass, as a casual US finding or is revealed by a scrotal trauma [48]. Scrotal pain may be the first symptom in 20% of cases and it is present in up to 27% of patients with TC [48, 49]. 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 [49].

Diagnosis is delayed in around 10% of cases of testicular tumour that mimic orchioepididymitis [49], 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. US must be performed in any doubtful case. A correct diagnosis must be established in all patients with an intrascrotal mass [50].

5.2   Imaging of the testis

Currently, US serves to confirm the presence of a testicular mass and to explore the contralateral testis. US sensitivity is almost 100%, and US has an important role in determining whether a mass is intra- or extratesticular [51]. US is an inexpensive test and should be performed even in the presence of clinically evident testicular tumour [52].

US 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 [53, 54].

MRI 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 [51, 55].

5.3 Serum tumour markers at diagnosis

Serum tumour markers are prognostic factors and contribute to diagnosis and staging [56]. The following markers should be determined before, and 5-7 days after, orchiectomy:
- AFP (produced by yolk sac cells);
- hCG (expression of trophoblasts);
- LDH (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 [48, 57]. AFP 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 [26].

Lactase dehydrogenase (LDH) is a less specific marker, its concentration being proportional to tumour volume. Its level may be elevated in 80% of patients with advanced TC [26]. 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 [58].

Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research.

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.

In cases of life threatening disseminated disease, lifesaving chemotherapy should be given up-front, especially when the clinical picture is very likely testicular cancer 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 30% of the testicular volume and surgical rules are respected. In those cases, the rate of associated TIN 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 cm^2 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 [25]:
  - 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 (TIN/ITGCN) in non-tumour parenchyma.
- pT category according to TNM 2009 [44].
- 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 Diagnosis and treatment of testicular intraepithelial neoplasia (TIN)

Contralateral biopsy has been advocated to rule out the presence of TIN [59]. Although routine policy in some countries, the low incidence of TIN and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively) [60, 61], the morbidity of TIN 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 [62, 63].

It is still difficult to reach a consensus on whether the existence of contralateral TIN must be identified in all cases. However, biopsy of the contralateral testis should be offered to patients at high risk for contralateral TIN, 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 [31, 46, 64-66]. A double biopsy increases sensitivity [65]. Patients should be informed that a testicular tumour may arise in spite of a negative biopsy [67].

Once TIN 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 [32, 62, 68, 69]. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US [65].

If TIN 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%) [70].

5.8 Screening

There are no high level evidence studies proving the advantages of screening programmes, but it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, self-physical examination by the affected individual is advisable.

5.9 Guidelines for the diagnosis and staging of testicular cancer

Recommendations	GR
Perform testicular US 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 TIN,	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 (AFP, hCG, and LDH), both before and 5-7 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

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase;
TIN = testicular intraepithelial neoplasia.

6. PROGNOSIS

6.1 Risk factors for metastatic relapse in NSGCT 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 [71]. However, these risk factors have not been validated in a prospective setting except that the absence of both factors indicated a low recurrence rate (6%) [72]. 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 [73]. 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 [74].

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	• Tumour size (> 4 cm) • Invasion of the rete testis	• Vascular/lymphatic in or peri-tumoural 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 also impair fertility. 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 treatment [68, 75-77]. In cases of bilateral orchiectomy or low testosterone levels after treatment of TIN, life-long testosterone supplementation is necessary [78]. Patients with unilateral or bilateral orchiectomy should be offered a testicular prosthesis [79]. For more detailed information, the reader is referred to the EAU Male Infertility Guidelines [80].

7.2 Stage I Germ cell tumours

7.2.1 Stage I seminoma

After modern staging procedures, about 15-20% of stage I seminoma patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone.

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 [81]. Previous analyses from four studies showed an actuarial 5-year relapse-free rate of 82.3%. The Princess Margaret Hospital series (n = 1559) showed an overall relapse rate in unselected patients of 16.8%. The actuarial relapse rate is in the order of 15-20% at 5 years, and most of the relapses are first detected in infra-diaphragmatic lymph nodes [82].

In patients with low risk (tumour size ≤ 4 cm and no rete testis invasion), the recurrence under surveillance is as low as 6% [83]. 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 [84]. 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 [82, 84]. 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 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 4 years [85-87]. Therefore, adjuvant carboplatin therapy using a dosage of one course of AUC 7 is an alternative to radiotherapy or surveillance in stage I seminoma [82, 85-87]. Two courses of adjuvant carboplatin seem to further reduce the relapse rate to the order of 1-3% [72, 88], but additional experience and long-term observation is needed.

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% [89-91]. Adjuvant irradiation of supradiaphragmatic lymph nodes is not indicated in seminoma stage I.

With regard to the irradiation dose, a large MRC randomised trial of 20 Gy vs. 30 Gy PA radiation in stage I seminoma showed equivalence for both doses in terms of recurrence rates [90]. 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% [89]. The main concern surrounding adjuvant radiotherapy is the increased risk of radiation-induced second non-germ cell malignancies [92-94].

A scrotal shield should be considered during adjuvant radiotherapy in order to prevent scattered radiation toxicity in the contralateral testis [92].

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 group of 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 [71]. A prospective trial based on no risk factors, surveillance, both risk factors and two courses of carboplatin AUC 7 showed the feasibility of a risk-adapted approach. Early data with limited follow-up indicate that patients without either risk factor have a very low risk, 6.0% - 14.8%, of relapse at 5 years. Patients in the high-risk group treated with carboplatin experienced a 1.4% - 3.2% relapse rate at mean follow-up of 34 months [83, 95].

7.2.1.5   Retroperitoneal lymph node dissection (RPLND)

In a prospective, non-randomised study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of retroperitoneal relapses (9.5%) after RPLND as primary treatment. Therefore, RPLND is not recommended in stage I seminoma [93].

7.2.2   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 AUC 7, if carboplatin-based chemotherapy is considered.	A
Do not perform adjuvant treatment in patients at very low risk.	A
Do not perform radiotherapy as adjuvant treatment.	A

AUC = area under curve.
*Upgraded following panel consensus.

7.3   NSGCT clinical stage I

Up to 30% of NSGCT patients with clinical stage I (CS1) disease have subclinical metastases and will relapse if surveillance alone is applied after orchiectomy. 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.

7.3.1   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 12 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 [96, 97]. Approximately 35% of relapsing patients have normal levels of serum tumour markers at relapse, with 60% of relapses occuring 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 [98] 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 clinical stage I non-seminoma as long as they are compliant and informed about the expected recurrence rate as well as the salvage treatment [99, 100].

7.3.2 Adjuvant chemotherapy

Patients with CS1 NSGCT have a 14-48% risk of recurrence within 2 years after orchiectomy. Adjuvant chemotherapy with two courses of cisplatin, etoposide, and bleomycin (BEP) was introduced in 1996 by a prospective MRC trial [101]. Subsequently, adjuvant chemotherapy was mainly given in high risk patients (vascular invasion present) [101-103]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [101], 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 [104]. 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 [105]. This should be taken into consideration during decision-making.

In 2008, the German Testicular Study Group reported a randomised trial of nerve-sparing RPLND or one course of BEP as adjuvant treatment in CS 1 NSGCT without risk-adaption. Adjuvant chemotherapy significantly increased the 2-year recurrence-free survival rate to 99.41% (CI: 95.87%, 99.92%) as opposed to surgery, which had a 2-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) [106].

In a community-based prospective study, SWENOTECA recommended one course of BEP in LVI+ patients., while patients with LVI- chose between surveillance and BEP x 1 [107]. The relapse-rate of the 490 patients who received BEP x 1 at 5 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 [108]. 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 [110].

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 [111]. 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 [112].

7.3.3 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 [101-103, 107, 108, 113-115].

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 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.

7.3.4 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 of the German Testicular Cancer Study group 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 [106].

When RPLND is performed in a multicentre setting, higher rates of in-field recurrences and complications were reported [106, 116]. 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 [116, 117]. If no retroperitoneal metastases are found at RPLND (PS1), approximately 10% of the PS1 patients relapse at distant sites [73, 117]. If metastases are present and not treated with adjuvant chemotherapy, recurrence will occur in 31% of patients [117].

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 [117, 118].

The follow-up after RPLND is simpler and less costly than that carried out during post-orchiectomy surveillance because of the reduced need for abdominal CT scans [119]. 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 [120].

7.3.5 Guidelines for the treatment of stage 1 NSGCT

Recommendations	LE	GR
Inform patients with stage 1 NSGCT about all adjuvant treatment options after orchiectomy (surveillance, adjuvant chemotherapy, and 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 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 IGCCCG classification, followed by post-chemotherapy retroperitoneal lymph node dissection if necessary.	2a	A

Upgraded following panel consensus.
NSGCT = non-seminomatous germ cell tumou; RPLND = retroperitoneal lymph node dissection;
BEP = cisplatin, eposide, bleomycin; IGCCCG = International Germ Cell Cancer Collaborative Group.

7.3.6 Risk-adapted treatment for clinical stage 1 based on vascular invasion

Stage 1A (pT1, no vascular invasion): low risk	LE	GR
Offer surveillance if the patient is willing and able to comply.	2a	A
In low-risk patients not willing (or suitable) to undergo surveillance, offer adjuvant chemotherapy with one course of BEP.	2a	A*
Stage 1B (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 or nerve-sparing RPLND in high-risk patients not willing to undergo adjuvant chemotherapy. If pathological stage II is revealed at RPLND, discuss further chemotherapy as well as observation with the patient.		A*

Upgraded following panel consensus.
BEP = cisplatin, eposide, bleomycin; IGCCCG = International Germ Cell Cancer Collaborative Group;
NSGCT = non-seminomatous germ cell tumour; RPLND = retroperitoneal lymph node dissection.

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 [121]*
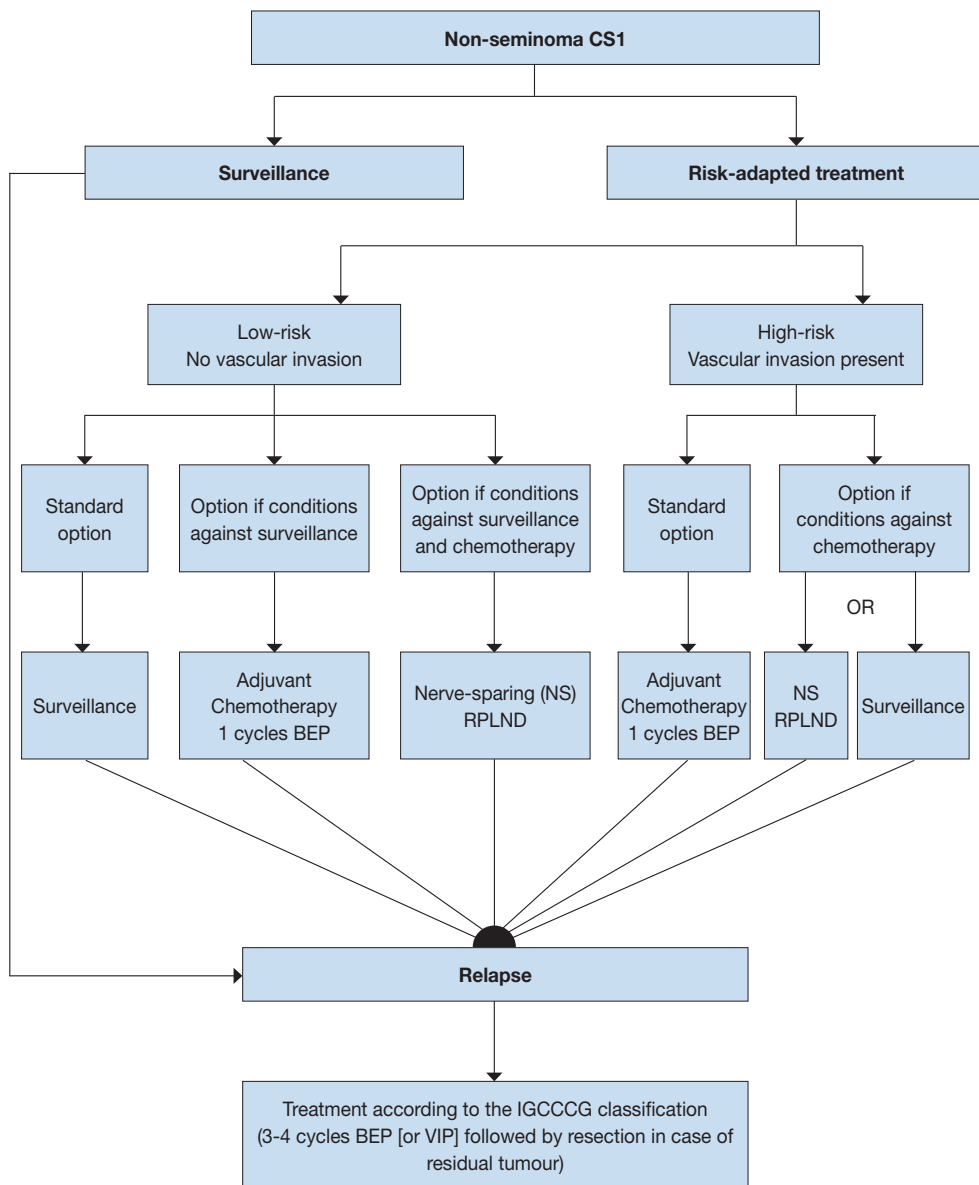
*All treatment options will need discussing with individual patients, to allow for them to make an informed decision as to their further care.
BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

7.4 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) [27].

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.

7.4.1 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. If the marker level increases after orchiectomy, the patient has residual disease. If RPLND is performed, up to 87% of these patients have pathologically documented nodes in the retroperitoneum [122]. An US examination of the contralateral testicle must be performed, if this was not done initially.

The treatment of true CS1S patients is still controversial. They may be treated with BEP x 3 chemotherapy and with follow-up as for CS1B patients (high risk, see below) after primary chemotherapy [123], or by RPLND [112].

7.4.2 *Metastatic disease (stage IIA/B)*

7.4.2.1 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 8 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).

So far, the standard treatment for stage IIA/B seminoma has been radiotherapy with reported relapse rates of 9-24% [124, 125]. 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. 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 [126]. The radiation dose delivered in stage IIA and IIB is approximately 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. Overall survival is almost 100% [124, 125]. Conversely, dose reduction to 27 Gy has been associated with 11% of relapses [84, 126].

In stage IIA/B cases, chemotherapy with 3 courses of BEP or 4 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. Although more toxic in the short term, BEP x 3 or EP x 4 achieve a similar level of disease control [127]. One population-based study with 67 stage IIB patients reported a relapse free-survival of 100% after a median follow-up of 5.5 years [84]. Single-agent carboplatin is not an alternative to standard EP or BEP chemotherapy for metastatic disease [128]. In CS IIA patients with seminoma, enrollment in clinical trials offering treatment options with potentially lower toxicity as compared to either radiotherapy or chemotherapy with 3 cycles BEP is recommended.

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B
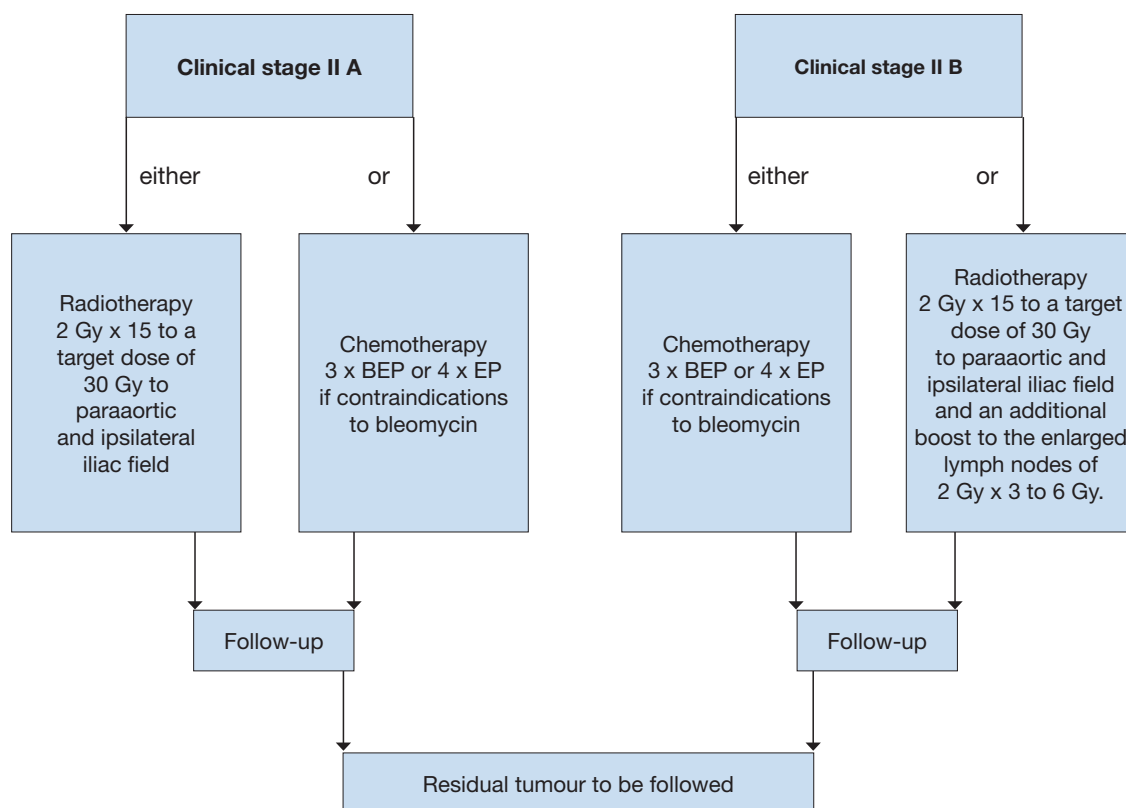
BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

7.4.2.2   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 [111, 129].

If surveillance is chosen, one follow-up evaluation after 6 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 beta-hCG, RPLND represents the first treatment option and should be performed by an experienced surgeon because of suspected viable disease or teratoma [129]. Patients with a growing lesion and a concomitant increase in the tumour markers AFP or beta-hCG require primary chemotherapy with BEP according to the treatment algorithm for patients with metastatic disease and IGCCCG recommendations (Figure 2). An alternative to the surveillance strategy in marker-negative II A/B non-seminoma with suspicion of an undifferentiated malignant tumour is a CT-guided biopsy, if technically possible. There is insufficient published data on PET scans in this situation.

When primary chemotherapy is refused by the patient or when it has some contraindications, primary nerve-sparing RPLND represents a viable option.

Primary chemotherapy and primary RPLND are comparable options in terms of outcome, but side-effects and toxicity are different, allowing for involvement of the patient in selecting the treatment of choice [130]. The cure rate with either approach will be close to 98% [131-133].

In patients with marker negative CS IIA follow up is only recommended, if teratoma is more likely than marker negative embryonal carcinoma. If possible, a biopsy is recommended to exclude marker negative embryonal carcinoma.

Figure 3 presents the treatment options for patients with NSGCT CS IIA.

Figure 3: Treatment options in patients with non-seminoma clinical stage IIA
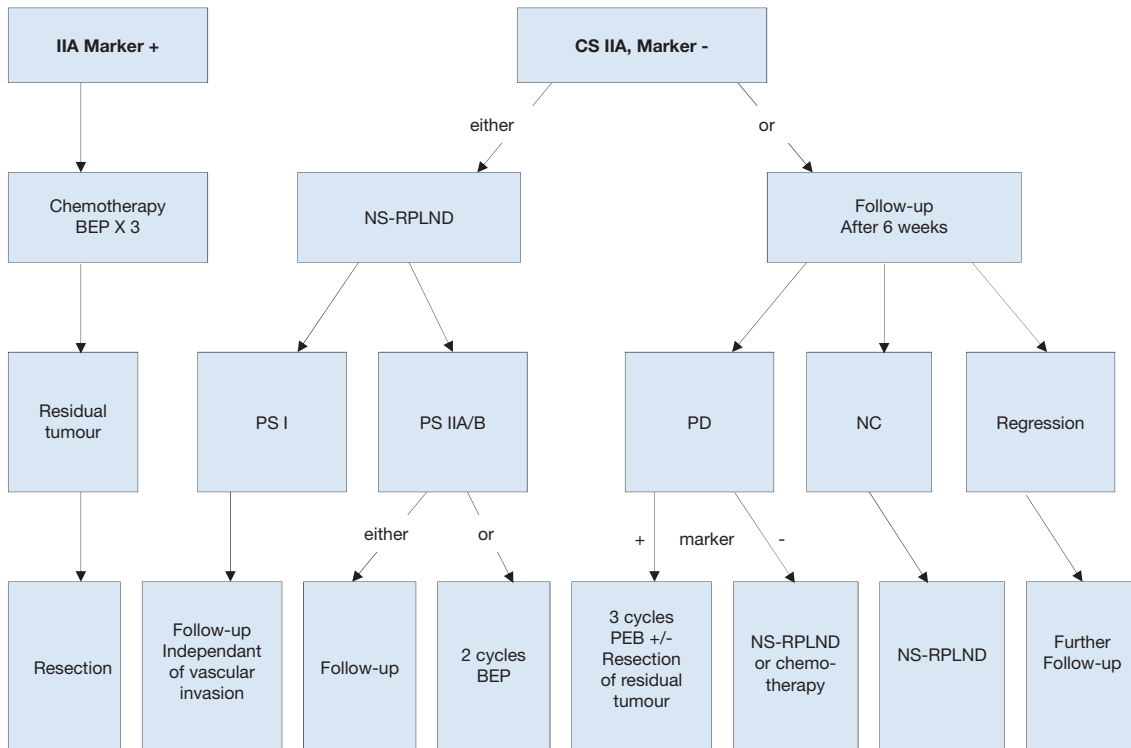
BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.

7.4.3 Metastatic disease (stage IIC and III)

7.4.3.1 Primary chemotherapy

7.4.3.1.1 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 [134]. Recent data indicate that EP x 4 results in cure in almost all cases of good-prognosis seminomatous germ cell cancers [135]. 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 [136]. Post-chemotherapy masses should be managed as described in Section 7.5.2.

7.4.3.1.2 Intermediate prognosis risk group - SGCT

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 [137].

7.4.3.1.3 Good prognosis risk group - NSGCT

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 [138, 139]. While data support a 3-day regimen of administering combination chemotherapy to be equally effective as a 5-day regimen, this is associated with increased toxicity when four cycles are used [140], thus the 5-day BEP regimen is recommended.

Table 7.1: 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.
BEP = cisplatin, etoposide, bleomycin.

In selected cases where bleomycin is contraindicated, EP x 4 can be given [27, 139]. A randomised trial from the French Groupe d'Etude des Tumeurs Genito-Urinaires (GETUG) suggested that when the BEP is used in this setting the mortality rate was half that of EP, although the difference did not reach statistical significance [141].

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 < 1000/mm^3 or thrombocytopaenia < 100,000/IU. 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 [142].

7.4.3.1.4 Intermediate prognosis risk group - NSGCT

The 'intermediate prognosis' group in the IGCCCG has been defined as patients with a 5-year survival rate of about 80%. The available data support BEP x 4 as standard treatment [27, 143]. A randomised trial compared BEP x 4 to BEP x 4 with the addition of paclitaxel (T-BEP) with no significant improvement in OS [144]. The overall toxicity with T-BEP was higher than with BEP, therefore it cannot be recommended as a standard approach.

7.4.3.1.5 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 [145, 146]. The 5-year progression-free survival is between 45% and 50%. Three randomised trials have shown no advantage in OS for high-dose chemotherapy in the overall 'poor prognosis' patients group [147-149]. However, patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [29, 147]. An online calculator is available for free 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 [30]. 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 [150]. Further prospective trials /registries are planned to validate this approach further.

Since a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [29, 151], 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 [11, 152]. 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 [153, 154].

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 3 days of EP without bleomycin) was suggested to reduce the risk of early death in this setting [153].

7.5 Restaging and further treatment

7.5.1 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) [27, 155, 156]. 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 [157].

Only with documented marker increase after two courses of chemotherapy is an early crossover of therapy to a completely new regimen indicated. These patients are usually candidates for new drug trials [158]. 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 [159, 160].

7.5.2 Residual tumour resection

7.5.2.1 Seminoma

A residual mass of seminoma should not be primarily resected, irrespective of the size, but controlled by imaging investigations and tumour markers [161-164].

FDG-PET 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 [40].

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 6 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) [165-167]. 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 [166]. Ejaculation may be preserved in these cases [168].

7.5.2.2 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 [169]. FDG-PET is not indicated to re-stage patients after chemotherapy [42]. In cases of complete remission after first line chemotherapy (no visible tumour), tumour resection is not indicated [170, 171]. Residual tumour resection is mandatory in all patients with a residual mass > 1 cm in the short axis at cross-sectional CT imaging [172-175].

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 [176].

Proponents of PC-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 [177]. 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 [170, 171]. 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 [171], 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 [178]. Therefore, there is an indication to perform surgery in salvage patients even with residual disease < 1 cm [170, 171].

If residual surgery is indicated, all areas of primary metastatic sites must be completely resected within 2-6 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 [171, 176, 179-182].

In persistent larger volume retroperitoneal disease, all areas of primary metastatic sites must be completely resected within 2-6 weeks of completion of chemotherapy. If technically feasible, a nerve-sparing procedure should be performed [171, 176, 179]. 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 [183-185].

7.5.3 *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 [172]. 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 [186].

Resection of contralateral pulmonary lesions is not mandatory in cases where pathologic examination of the lesions from the first lung show complete necrosis. However, disconcordant histologies between both lungs may occur in up to 20% of patients [187, 188].

7.5.3.1 *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 preformed and followed by ad hoc reconstructive surgery (e.g. vascular interventions such as vena cava or aortic prostheses) [189, 190]. In patients with intermediate or poor risk and residual disease > 5 cm the probability of vascular procedures is as high as 20% [191]. This surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Patients treated within such centres benefit from a significant reduction in perioperative mortality from 6% to 0.8% [12]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [13].

7.5.3.2 *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 [192]. Also, in the case of extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [193, 194].

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 [195].

7.5.3.3 *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) [180] (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 [196]. 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 [197].

7.5.4 **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 [198]. 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) [199]. No randomised trial has ever 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 3 cycles of vinblastine, ifosfamide, and cisplatin (VeIP) plus 1 cycle of consolidation high-dose chemotherapy, compared with VeIP x 4 [200]. At present, it is impossible to determine whether conventionally dosed cisplatin based combination chemotherapy is sufficient as first-salvage treatment or whether early intensification of first-salvage treatment with high-dose chemotherapy should be used. However, there is evidence from large retrospective analyses that there are different prognostic groups in the case of relapse after first-line chemotherapy [201-203], and the Lorch-Beyer score has resulted in 5 prognostic subgroups (Table 7.3).

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 is planned (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 [204].

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
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

PEI/VIP = cisplatin, etoposide, ifosfamide; TIP = paclitaxel, ifosfamide, cisplatin; GIP = gemcitabine, ifosfamide, cisplatin

* Plus hydration.

† Plus mesna protection.

^{xx} An MRC schedule uses paclitaxel at 175 mg/m^2 in a 3 hour infusion [205].

The International Prognostic Factors Study Group score comprised of 7 important factors is listed in Table 7.3 (seminoma vs. non-seminoma histology, primary tumour site, response to initial chemotherapy, duration of progression-free interval, AFP marker level at salvage, hCG marker level at salvage, and the presence of liver, bone, or brain metastases at salvage). 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 $\geq$ 5 points) were identified with significant differences in PFS and OS. Table 4.3 illustrates the 5 risk groups and the corresponding 2-year PFS and 3-year OS rates [206].

Table 7.3: The International Prognostic Factors Study Group Score Construction [202]

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; PFI = progression-free interval.

Table 7.4: PFS and OS estimates for all patients according to IGCCCG-2 prognostic score [202]

	N	%	HR	2-years PFS	3-year OS
Score n = 1435					
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				

IGCCCG = International Germ Cell Cancer Collaborative Group; OS = overall survival; PSF = progression-free survival.

7.5.5 *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 [202]. Even with HD-therapy the chance of cure is only 20-25%.

Refractory disease: Patients relapsing within 4-8 weeks after platinum-based therapy or who are progressing despite platinum-based therapy as well as those relapsing shortly after HD chemotherapy are considered cis-platinum 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%. Cisplatin re-challenge in association with gemcitabine and paclitaxel, could be considered in patients with good renal function [207].

Patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15-20% chance of long-term cure [193].

7.5.5.1 *Late relapse (≥ 2 years after end of first-line treatment)*

Late relapse is defined as recurrence more than 2 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 [208, 209]. 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 [109, 210, 211].

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 [212].

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 [213]. 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 [214].

7.5.5.2   Treatment of brain metastases
Brain metastases occur in the frame of 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 5-year survival-rate is 2-5%) [215, 216]. Chemotherapy is the initial treatment in this case, and some data support the use of consolidation radiotherapy, even in the case of a total response after chemotherapy [217]. 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.

7.5.6   Guidelines for the treatment of metastatic germ cell tumours

Recommendations	LE	GR
Treat low volume NSGCT stage IIA/B with elevated markers like 'good or intermediate prognosis' advanced NSGCT, with three or four cycles of BEP.	2	A
In stage IIA/B NSGCT without marker elevation, exclude marker negative embryonal carcinoma by obtaining histology by either RPLND or biopsy. If not possible, repeat staging after 6 weeks of surveillance before making a final decision on further treatment.	3	B
In metastatic NSGCT (≥ stage IIC) with good prognosis, treat with three courses of BEP.	1	A
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 3 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
Treat seminoma CSII A/B initially with radiotherapy. When necessary, use chemotherapy as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.	2	B
In seminoma stage CS IIA/B, offer chemotherapy (BEP x 3 or EP x 4, in good prognosis) as an alternative to radiotherapy.	1	A
Treat seminoma stage IIC and higher with primary chemotherapy according to the same principles used for NSGCT.	1	A

EP = eposide, cisplatin; GR = grade of recommendation; NSGCT = non-seminomatous germ cell tumour; BEP = cisplatin, eposide, bleomycin; RPLND = retroperitoneal lymph node dissection.

8.   FOLLOW-UP AFTER CURATIVE THERAPY

8.1   Follow-up care for cancer patients
There is no consensus on a standardised follow-up of patients treated for germ-cell cancer.

8.2   General considerations
The following considerations apply in a general manner for the selection of an appropriate schedule and testing in the follow-up of all stages of testis tumour.
- Most recurrences after curative therapy will occur in the first 2 years; surveillance should therefore be most frequent and intensive during this time.
- Late relapses can occur beyond 5 years, and therefore yearly life-long follow-up may be advocated.
- After RPLND, relapse in the retroperitoneum is rare, the most likely site of recurrence being the chest.
- The value of a plain radiography chest has been recently questioned in the follow-up of patients with disseminated disease after complete remission [218, 219].
- CT of the chest has a higher predictive value than plain radiography chest [219].
- The results of therapy are dependent on the bulk of disease; therefore, an intensive strategy to detect asymptomatic disease may be justifiable.

- After chemotherapy or radiotherapy, there is a long-term risk of the development of secondary malignancies.
- Exposure to diagnostic X-rays causes second malignancies [220]. Therefore, the frequency of CT scans should generally be reduced and any exposure to X-rays should be well justified in a patient cohort with a very long life-expectancy after successful treatment.
- CT can be substituted by MRI however, MRI is a protocol-dependent method and should be performed in the same institution with a standardised protocol.
- With special expertise, US may be used as a method to screen the retroperitoneum during follow-up. However, the method is very much dependent on the investigator and cannot be recommended as the standard method during follow-up.
- Longer follow-up in patients after radiotherapy and chemotherapy is justified to detect late toxicities (e.g. cardio-vascular, endocrine).

A number of interdisciplinary organisations have presented recommendations for follow-up of TC patients [221-223]. The follow-up tables below (Tables 8.1 through 8.4) present the minimum recommendations based on the expert opinions of the guideline authors.

8.3 Follow-up: stage I non-seminoma

Approximately 5% of patients with CS1 NSGCT present with elevated levels of tumour markers after orchiectomy, and 25-30% relapse during the first 2 years [102, 224-226]. The follow-up schedule will differ depending on which of the three possible treatment strategies was chosen:
- surveillance;
- nerve-sparing RPLND;
- adjuvant chemotherapy.

8.3.1 Follow-up investigations during surveillance

The results of a surveillance policy depend upon a careful pre-operative staging procedure and follow-up management. In a 'wait and see' policy, relapses will occur in 30% of cases. Of these relapses, 80% will occur in the first 12 months after orchiectomy, and approximately 12% during the second year. The median time to relapse is 6 months, but relapses after 3-5 years, and even later, can still occur, with an annual rate of 4% [90, 91]. Relapse occurs mainly in the retroperitoneum: approximately 70% of patients have evident metastases in the retroperitoneum, and 10% in the mediastinum and lungs [227]. Sometimes the only indication is an elevated level of tumour markers.

A randomised trial of two vs. five CTs has been published by the MRC, which recommends the reduction of imaging during surveillance in this stage, to one CT scan at 3 months after orchiectomy, and another at 12 months. The trial, with a cohort of 414 patients, was powered to exclude a 3% probability of detecting a patient during surveillance only, with a relapse presenting already-metastatic disease with 'intermediate' or 'poor' prognosis features. Relapses were detected in 15% with two CT, and 20% with five CT; 1.6% of these patients had 'intermediate' or 'poor' prognostic features. Only 10% of patients had high-risk features (vascular invasion). In summary, this first randomised trial yielded level 1 evidence for a minimum follow-up in patients with CS1 non-seminoma [115]. The recommended follow-up schedule (Table 8.1) includes the minimum requirements for imaging, and adds recommendations for other surveillance tests [227].

Table 8.1: Recommended minimum follow-up schedule in a surveillance policy: stage I non-seminoma [227]

Procedure	Year			
	1	2	3	4-5
Physical examination	4 times	4 times	4 times	Once/year
Tumour markers	4 times	4 times	4 times	Once/year
Plain radiography chest	Twice	Twice	Twice	Twice
Abdominopelvic CT	Twice at 3 and 12 months	Once at 24 months	Once at 36 months	

CT = computed tomography.

8.3.2 Follow-up after nerve-sparing RPLND

Retroperitoneal relapse after a properly performed nerve-sparing RPLND is rare. RPLND should eliminate the retroperitoneal nodes as a site of relapse and thus the need for repeated abdominal CTs. The USA Testicular Cancer Intergroup study data showed retroperitoneal relapse in 7/264 patients with pathological stage I disease

and 20 pulmonary relapses. Four of these seven had no marker elevation [228]. In the Indiana series, only one relapse in 559 cases was reported [229]. If a relapse occurs, it is generally in the chest, neck or at the margins of the surgical field.

Pulmonary relapses occur in 10-12% of patients, and more than 90% of those relapses occur within 2 years of RPLND [45, 230]. However, the low rate of retroperitoneal relapse after RPLND can only be achieved by surgery in specialised centres, as shown by the high in-field relapse rate (7/13 relapses) in the German randomised trial of RPLND vs. BEP x 1 [106]. The recommended minimum follow-up schedule is shown in Table 8.2.

Table 8.2: Recommended minimum follow-up schedule after retroperitoneal lymphadenectomy or adjuvant chemotherapy: stage I non-seminoma

Procedure	Year				
	1	**2**	**3**	**4-5**	**6-10**
Physical examination	4 times	4 times	4 times	Once/year	Once/year
Tumour markers	4 times	4 times	4 times	Once/year	Once/year
Plain radiography chest	Twice	Twice	Twice		
Abdominopelvic CT	Once	Once	Once	Once/year	

CT = computed tomography.

8.3.3 *Follow-up after adjuvant chemotherapy*
Prospective reports with long-term follow-up after adjuvant chemotherapy have shown a low relapse rate of about 3% [102]. In a randomised trial with one course of BEP vs. RPLND, the relapse rate with adjuvant chemotherapy was 1% (2/174 patients, one with marker relapse, one with mature teratoma in the retroperitoneum) [106]. The need for repeated and long-term assessment of the retroperitoneum is still not clear. Owing to the risk of developing a late, slow-growing teratoma in the retroperitoneum after adjuvant chemotherapy, an abdominal CT should still be performed (see Table 8.2).

8.4 Follow-up: stage I seminoma
The majority of patients with seminoma (70-80%) present with clinical stage I disease at diagnosis. In 15-20% of cases there is nodal radiological involvement at the level of the retroperitoneum and only 5% of patients present with distant metastasis.

The relapse rate varies between 1% and 20% depending on the post-orchiectomy therapy chosen. Up to 30% of seminomas present with elevation of hCG at diagnosis or in the course of the disease. Consequently, in most cases, measurement of blood markers will not be a reliable test for follow-up [231]. The treatment options post-orchiectomy in stage I seminoma are surveillance or adjuvant carboplatin chemotherapy.

8.4.1 *Follow-up after radiotherapy*
Low doses of radiotherapy (20-24 Gy) limited to the retroperitoneal or the para-aortic and ipsilateral field achieve an OS rate of approximately 99% at 5-10 years [90, 91, 232, 233]. The rate of relapse is 1-2% and the most common time of presentation is within 18 months of treatment [90, 233-235], although late relapses have also been described [210]. The site of relapse is mainly at the supradiaphragmatic lymph nodes, mediastinum, lungs or bones. In a small proportion of cases, the tumour will relapse in the inguinal or external iliac nodes. After para-aortic field RT there is also a pelvic node relapse pattern.

The side-effects of radiotherapy include temporary impaired spermatogenesis, GI symptoms (peptic ulceration), and induction of second malignancies [234, 236, 237]. Up to 50% of patients can develop moderate toxicity grade I-II [231]. The follow-up schedule is described in Table 8.3.

Table 8.3: Recommended minimum follow-up schedule for post-orchiectomy surveillance, radiotherapy or chemotherapy: stage I seminoma [226]

Procedure	Year		
	1	**2**	**3-5**
Physical examination	3 times	3 times	Once/year
Tumour markers	3 times	3 times	Once/year
Plain radiography chest	Twice	Twice	
Abdominopelvic CT	Twice	Twice	at 36 and 60 months

CT = computed tomography.

8.4.2   Follow-up during surveillance
The actuarial risk of relapse at 5 years ranges between 6% and 20% [92, 238-242]. There is no increased risk of death. The median time to relapse ranges from 12-18 months, but up to 29% of relapses can develop later than this [81, 243]. The sites of relapse are the PA lymph nodes in up to 82% of cases, the pelvic lymph nodes, inguinal nodes and lungs can also be affected [81, 105, 244-247]. Due to the high and often late rate of relapse, close and active follow-up is mandatory for at least 5 years [238] (see Table 8.3).

8.4.3   Follow-up after adjuvant chemotherapy
One or two courses of carboplatin-based chemotherapy is an effective alternative treatment in stage I seminoma. The relapse rate is 1.9-4.5%. In general, this treatment is well tolerated, with only mild, acute and intermediate-term toxicity [238, 239]. Long-term data on late relapses and survival are missing (see Table 8.3).

8.5   Follow-up: metastatic disease
The more advanced the nodal stage of the disease, the higher the likelihood of recurrence [131]. In general, the primary tumour bulk governs the outcome for patients with NSGCT [243]. In stage II NSGCT, regardless of the treatment policy adopted, excellent survival rates of 97% are reached provided that relapse is identified as soon as possible [111, 132].

In advanced metastatic germ-cell tumours, the extent of the disease correlates with the response to therapy and with survival. The combination of cisplatin-based chemotherapy and surgery (aggressive multimodality) achieves cure rates of between 65% and 85%, depending on the initial extent of disease [241, 242]. Complete response rates to chemotherapy are in the order of 50-60% [241]; another 20-30% of patients could be disease-free with post-chemotherapy surgery [248].

The main reasons for failure of therapy in advanced NSGCT are [27, 240, 249]:
*   the presence of bulky disease not responding completely to chemotherapy;
*   unresectable residual teratoma after chemotherapy;
*   the presence or development of chemoresistant non-germ elements, which account for 8.2% of cases.

Table 8.4 presents the recommended minimum follow-up schedule in advanced NSGCT and seminoma.

Table 8.4: Recommended minimum follow-up schedule in metastatic NSGCT and seminoma

Procedure	Year			
	1	2	3-5	Thereafter
Physical examination	4 times	4 times	Twice/year	Once/year
Tumour markers	4 times	4 times	Twice/year	Once/year
Plain radiography chest	4 times	4 times	Twice/year	Once/year
Abdominopelvic CT*	Twice	Twice	Once/year	As indicated
Chest CT†‡	Once/year	Once/year	Once/year	As indicated
Brain CT§	Once/year	Once/year	Once/year	As indicated

CT = computed tomography.
* An abdominal CT must be performed at least annually if teratoma is found in the retroperitoneum.
† If the post-chemotherapy evaluation in a seminoma patient shows any mass > 3 cm, the appropriate CT should be repeated 2 and 4 months later to ensure that the mass is continuing to regress. If available, FDG-PET/CT can be performed.
‡ A chest CT is indicated if abnormality is detected on a plain radiography chest and after pulmonary resection.
§ In patients with headaches, focal neurological findings, or any central nervous system symptoms.

8.6   Quality of life and long-term toxicities after cure for testicular cancer
The vast majority of patients will be cured and 5-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 [250]. 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 [100], 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 [251]. 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 [102, 110, 252].

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 [208, 253]. The following overview is not complete and interested readers are referred to review articles on this topic [250, 253, 254].

8.6.1 Second malignant neoplasms (SMN)
Treatment-induced SMN usually occur after the first 10 years [253]. The risk for solid SMN increases with younger age at radio- or chemotherapy and remains significantly elevated for at least 35 years [93, 255-257]. RT-related SMN are primarily localised within or close to the RT field (colon, stomach, pancreas, bladder and the urinary tract) [93, 94, 256-259]. Fung *et al.* demonstrated that modern cisplatin-based chemotherapy was associated with a 40% increased risk of a solid SMN [260].

8.6.2 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 [261]. The risk of AML seems to be both related to the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m^2 have been shown to increase the subsequent risk of AML [262]. 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 10 years after treatment for TC and has a very poor prognosis [263].

8.6.3 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) [264]. 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.

8.6.4 Pulmonary complications
Chemotherapy exposed TCSs have a nearly 3-fold increased risk of dying of pulmonary diseases than the normal population [264]. Bleomycin-induced lung toxicity may affect 7% to 21% of patients in the long term, resulting in death in 1%-3% [265]. TCSs treated with high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured by surgery only [266]. Intriguingly, pulmonary complications were associated with the cumulative cisplatin dose and not to the dose of bleomycin.

8.6.5 Cardiovascular toxicity
Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population [264, 267]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [105, 246]. The metabolic syndrome is a strong predictor for CVD and its components, hypertension, obesity and hypercholesterolemia, increase with treatment intensity [247, 268]. Circulating residual serum platinum might exert endothelial stress [269].

8.6.6 Raynaud-like phenomena
Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually ascribed to the application of bleomycin [270, 271]. Cisplatin is believed to contribute to cold-induced vasospasms, as 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 [272].

8.6.7 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 [273]. 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 [269].

8.6.8 Ototoxicity
Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly frequencies of 4000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [274-276]. Both hearing impairment and tinnitus are considerably increased after application of 50 mg/m^2 cisplatin over two days as compared to 20 mg/m^2 over five days (odds ratio 5.1 and 7.3, respectively), indicating a higher impact of serum peak concentrations than cumulative doses [273]. A significant association between glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [277, 278]. Hopefully, increasing insight into the pathogenesis of and vulnerability for this complication will lead to more individualised treatment in the future.

8.6.9 Nephrotoxicity
Cisplatin-based chemotherapy may lead to long-term renal function impairment in 20-30% of TCSs [273-276]. In TC patients, reduced renal elimination of cisplatin and bleomycin might increase the risk of other toxicities, e.g. bleomycin-related pneumonitis [279, 280].

8.6.10 Hypogonadism
Testicular endocrine dysfunction comprises insufficient testosterone (T) 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 [253, 281].

8.6.11 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 6 months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [282]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs at a median of 12 years after treatment for TC when compared with the age-matched Norwegian population (10%) [283]. Of note, the prevalence of CF increased from 15% to 27% during a 10 year period in long-term TCSs [284].

8.6.12 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 [285]. When comparing three or four cycles of BEP in good risk patients, all outcomes favour treatment with three courses [140]. 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 [286].

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 2004 (adapted) [25].

9.2   Leydig cell tumours
9.2.1 Epidemiology
Leydig cell tumours constitute about 1-3% of adult testicular tumours [287, 288] and 3% of testicular tumours in infants and children [288]. 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 3 and 9 years. Only 3% of Leydig cell tumours are bilateral [287]. These tumours occur in about 8% of patients with Klinefelter's syndrome [289].

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) [25].
Approximately 10% of Leydig cell tumours are malignant and present with the following parameters [290, 291]:
• 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 [292, 293], 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 [293, 294]. Only 3% of tumours are bilateral [287].

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 [295]. The proportion of metastatic tumours in all published case reports is less than 10%. In three old series with long follow-up, 18 metastatic tumours were found in a total of 83 cases (21.7%) [287, 290, 296], while 5 recently published studies with long follow-up reported only 2 metastatic tumours in 156 patients (1.3%) [293, 294, 297-299].

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 [300, 301]. 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 [300]. 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%) [300]. The rate of malignancy ranges between 10% and 22%. Signs of a malignant Sertoli tumour are as follows [302, 303]:
• 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 [301]:
• classic Sertoli cell tumour [300];
• large cell calcifying form with characteristic calcifications [304, 305];
• sclerosing form [306, 307].

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 [300]. 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 [301]. Only the large cell calcifying form has a characteristic image with bright echogenic foci due to calcification [308]. 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 [300].

The **large cell calcifying** form is diagnosed in younger men and is associated with genetic dysplastic syndromes (Carney's complex [309] and Peutz-Jeghers syndrome [310] 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 [305].
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%) [301].

The sclerosing subtype is very rare, unilateral, with a mean age around 40 years and metastases are infrequent [307].

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% [311]. 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 [312] or to achieve long-term cure in stage IIA cases [313]. Prophylactic RPLND is unjustified for patients with clinical stage I disease without high-risk features [314].
Tumours that have metastasised to lymph nodes, lung, liver or bone respond poorly to chemotherapy or radiation and survival is poor [312]. 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 3 to 6 months with physical examination, hormone assays, scrotal and abdominal ultrasonography, chest radiography, and CT [293].

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 prepubertal testicular neoplasms. The cystic appearance is characteristic of this tumour type [315, 316].
- 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 [317].

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 [318].

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 [319].

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 [32]. 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 [320].

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 [321, 322].

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 [323].

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 [25].

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 [324].

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.

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# 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/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
Penile Cancer

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European
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of Urology

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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.

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 paper 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 occurring 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 adding 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 2015.

2.3 Future Goals

The results of ongoing and new systematic reviews will be included in the 2017 update of the Penile Cancer Guidelines. These reviews are performed using standard Cochrane systematic review methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Ongoing systematic reviews:
1. What are the risks and benefits of primary radiation therapy vs. conservative surgery for penile cancer?
2. What are the risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy for penile cancer?

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 the 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 [6, 7], although there are several geographical areas in Europe with an incidence over 1.00/100,000 (Figure 1) [8]. In North America [6], 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 representing 1-2% [8] of malignant diseases in men.

Penile cancer is common in regions with a high prevalence of human papilloma virus (HPV) [6]. 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 [8, 9]. The majority of knowledge about penile cancer comes from countries with a high incidence.

The incidence of penile cancer is related to the prevalence of HPV in the population, which may account for the variation in incidence, as the worldwide HPV prevalence varies considerably. 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 [6]. In Europe, the overall incidence has been stable from the 1980s until now [7], with an increased incidence reported in Denmark [10] and the UK. A UK longitudinal study confirmed a 21% increase in incidence from 1979-2009 [11]. The incidence of penile cancer increases with age [7]. The peak age is during the sixth decade of life, though the disease does occur in younger men [12].

Figure 1: Annual incidence rate (world standardised) by European region/country*

Penis: ASR (World) (per 100,000) (All ages)
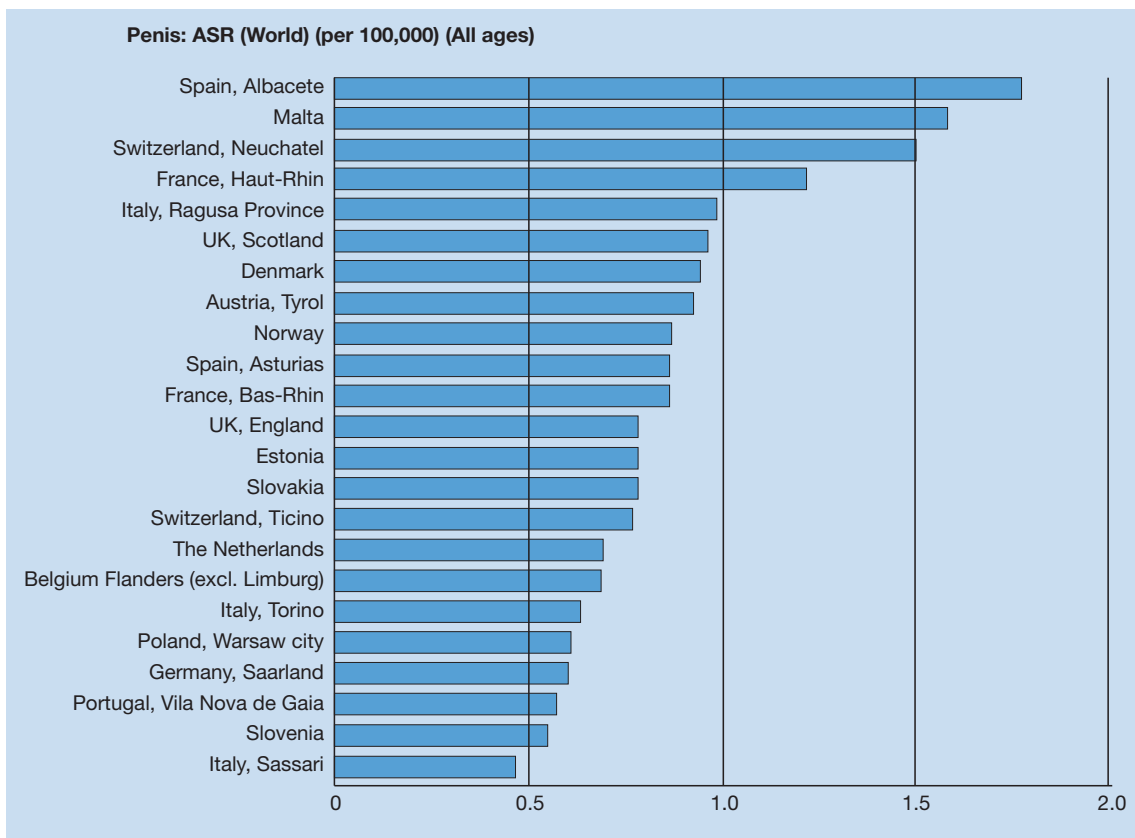
*Adapted from [8].

3.3 Risk factors and prevention

Review of the published literature from 1966-2000 identified several risk factors for penile cancer [13] (Table 1) (LE: 2a).

Table 1: Recognised aetiological and epidemiological risk factors for penile cancer

Risk factors	Relevance	Ref
Phimosis	OR 11-16 vs. no phimosis	[14, 15]
Chronic penile inflammation (balanoposthitis related to phimosis) Balanitis xerotica obliterans (lichen sclerosus)	Risk	[16]
Sporalene and UVA phototherapy for various dermatological conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments	[17]
Smoking	5-fold increased risk (95% CI: 2.0-10.1) vs. non-smokers	[14, 15, 18]
HPV infection condylomata acuminata	22.4% in verrucous SCC 36-66.3% in basaloid-warty	[6, 19]
Rural areas, low socioeconomic status, unmarried		[20-23]
Multiple sexual partners, early age of first intercourse	3-5-fold increased risk of penile cancer	[13, 15, 24]

HPV = human papilloma virus; OR = odds ratio; SCC = squamous cell carcinoma; UVA = ultraviolet A.

Human papilloma virus infection (HPV) is an important risk factor; HPV DNA was found in 70-100% of intraepithelial 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 [19] through interaction with oncogenes and tumour suppressor genes (P53, Rb genes) [25]. The commonest HPV subtypes in penile cancer are types 16 and 18 [26] and the risk of penile cancer is increased in patients with condyloma acuminata [27] (LE: 2b).

It remains unclear whether HPV-associated penile cancer has a different prognosis to

non-HPV-associated penile cancer. A significantly better 5-year disease-specific survival was reported for HPV-positive vs. HPV-negative cases (93% vs. 78%) [28], while others reported no difference in lymph node metastases and 10-year survival rates [29].

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 [30, 31]. 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 pattern in penile and cervical cancer. The epidemiological effects of HPV vaccination in girls are also awaited [32, 33].

Phimosis is strongly associated with invasive penile cancer [15, 20, 34, 35], probably due to associated chronic infection since smegma is not a carcinogen [34]. A further risk factor suggested by epidemiological studies is cigarette smoking (4.5-fold increased risk (95% CI: 2.0-10.1) [35]. 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 socioeconomic status and education [20].

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 [15]). Neonatal circumcision does not reduce the risk of CIS [15].

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) [36-39]. 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, these 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 SCC of the penis
•   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)
•   Intraepithelial neoplasia grade III
•   Giant condylomata (Buschke-Löwenstein)
•   Erythroplasia of Queyrat
•   Bowen's disease
•   Paget's disease (intradermal ADK)

Table 3: Histological subtypes of penile carcinomas, their frequency and outcome

Subtype	Frequency (% of cases)	Prognosis
Common SCC	48-65	Depends on location, stage and grade
Basaloid carcinoma	4-10	Poor prognosis, frequently early inguinal nodal metastasis [40]
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 [41] (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 HPV, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis [42]

3.4.1   Gross handling
Tissue sections must include entire small lesions and at least 3-4 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 because of its prognostic relevance (Table 4). Both Broder's classification and the WHO grading system for grading penile cancer are highly dependent on the observer and are no longer used [43].

3.4.4   Pathological prognostic factors
Carcinomas limited to the foreskin have a better prognosis and lower risk of regional metastasis [44]. Perineural invasion and histological grade are very strong predictors of poor prognosis and cancer-specific mortality [45]. 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 [46]. 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 3 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 [47] (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 [48].

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 [48] (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 [49].

Remaining tumours were intermediate-risk tumours with 33% developing metastases. Another study reported similar findings and recommended prophylactic lymphadenectomy for high-risk patients [50]. 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 5-year survival [51]. The lower the score, the higher the probability of 95% survival at 5 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 [52, 53]. Telomerase activity has been shown in invasive penile carcinoma [54], and some authors have shown that aneuploidy changed according to tumour grade [55].

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 [56]. Allelic loss of the p53 gene is a frequent event in penile SCC (42%) [57] and p53 expression has been linked to poor prognosis [58]. Another element influencing lymph node metastasis is the metastasis suppressor protein KAI1/CD82; decreased expression of this protein favours lymph node metastasis [59].

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 [36]. 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 assess properly 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 [60]. 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 [61].

4.   STAGING AND CLASSIFICATION SYSTEMS

4.1   TNM classification

The 2009 TNM classification [62] stratifies the T1 category into two prognostically different risk groups, depending on the presence or absence of lymphovascular invasion and grading (Table 4). The rationale for a potential further subdivision of the T2 category is discussed under Section 3.4.4 [47, 48].

The 2009 TNM classification recognizes the adverse effect of extracapsular spread on prognosis and therefore classifies any inguinal lymph node metastasis with extracapsular extension as pN3 [62]. Retroperitoneal lymph node metastases are extra-regional nodal and therefore distant metastases.

Table 4: 2009 TNM clinical and pathological classification of penile cancer [62]

Clinical classification	
T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
Ta	Non-invasive carcinoma
T1	Tumour invades subepithelial connective tissue
	T1a Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated or undifferentiated (T1G1-2)
	T1b Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated or undifferentiated (T1G3-4)
T2	Tumour invades corpus spongiosum and/or corpora cavernosa
T3	Tumour invades 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 node
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple unilateral 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	Intranodal metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral or bilateral or extranodal extension of any 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

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 [63, 64]. 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 [65, 66].

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 [67].
- Conventional computed tomography (CT) or MRI scans cannot detect micrometastases reliably [68].
- Imaging with [18]FDG-positron emission tomography (PET)/CT does not detect lymph node metastases < 10 mm [69, 70].

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 [71, 72]. 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 [18]FDG-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 [70, 73].

5.3 Distant metastases

An assessment of distant metastases should be performed in patients with positive inguinal nodes [74-76] (LE: 2b). CT of the abdomen and pelvis and a chest X-ray are recommended. Thoracic CT is more sensitive than chest X-ray. PET/CT is an option for identifying pelvic nodal and distant metastases in patients with positive inguinal nodes [77].

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 in lymph-node-positive patients [78].

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.
CT of chest, abdomen and pelvis is recommended for patients with inguinal lymph node metastasis.
MRI with artificial erection improves local staging for men being considered for organ preserving surgery.

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	
For physical examination of both groins, record number, laterality and characteristics of inguinal nodes and: • If nodes are not palpable, offer invasive lymph node staging in high-risk patients (*see* Section 6). • If nodes are palpable, stage with a pelvic CT or 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.	

MRI = magnetic resonance imaging; CT = computed tomography; PET = positron emission tomography.

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 [79].

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 [80]. 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 cardon dioxide (CO_2) laser treatment [81].

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 [82].

6.1.2 Treatment of invasive disease confined to the glans (category Ta/T1a)

A penis-preserving strategy is recommended (GR: C) for small and localised invasive lesions (Ta/T1a). It is mandatory to do a biopsy to confirm diagnosis prior to using conservative treatments (GR: C). 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 intraoperative assessment of surgical margins by frozen section is recommended (GR: C) as tumour-positive margins lead to local recurrence [83]. Total removal of the glans (glansectomy) and prepuce has the lowest recurrence rate for the treatment of small penile lesions (2%) [83]. Negative surgical margins are imperative when using penile-conserving treatments (GR: C) and a margin of 5 mm is considered oncologically safe [83, 84].

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 neodynium:yttrium-aluminum garnet (Nd:YAG) laser or a CO_2 laser [85-90]. Visualization may be improved by photodynamic diagnosis.

The results of CO_2 laser treatment have been reported by three studies all from the same institution [85-87]. Laser treatment was given in combination with radiotherapy or chemotherapy to patients with CIS or T1 penile cancers. Follow-up was 5 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 5 years of 10% with CIS (n = 106) and 16% with T1 (n = 78) tumours [85]. In all three series taken together, local recurrence ranged from 14% for CIS [87] to 23% for T1 tumours [86]. The reported rate of inguinal nodal recurrence after local CO_2 laser treatment was 0% [87] and 4% [86]. Secondary partial penectomy at 10 years was 3% and 10%, depending on the tumour (CIS vs. T1) and whether combination treatment had been given or not [85].

Four studies on the results of Nd:YAG laser treatment [88-91] reported on a total of 150 patients with a follow-up of at least 4 years. Local recurrence rates at last follow-up ranged across the four studies from 10% [88] to 48% [89]. In one study [90], recurrence-free survival rates were reported as 100%, 95% and 89% at 1, 2 and 5 years, respectively. Inguinal nodal recurrence was reported in 21% of patients [88]. Cancer-related deaths were reported in 2% [91] and 9% of patients [89], 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 4 years [88] and 95% [90] to 85% [92] at 7 years. The rate of secondary partial penectomy after initial Nd:YAG laser treatment was reported as 4% [90] and 45% [89], respectively. Complications, urinary and sexual function outcomes were assessed in only one study with 29 patients [88], 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 CO_2 laser, Nd:YAG laser, a combination of both, or a potassium titanyl phosphate (KTP) laser [93-96], 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 5 years was 95% in one study using the Kaplan-Meier method [94]. 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 5 years [95]. Local recurrence rates were 11% [95], 19% [94] and 26% [96]. In one study recurrence-free survival at 5 years was estimated to be 88% [94].

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 conus of excision. This technique has not been widely used. Only two studies reported a total of 66 patients [97, 98]. The original description [97] consisted of 33 consecutive patients treated between 1936 and 1986 and reported on 29 patients with at least 5 years follow-up. In each study there was one secondary penile amputation and one death from penile cancer. In Mohs series, 79% were cured at 5 years [97]. 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 [98]. The local recurrence rate was 32% in one series [98].

6.1.3.3 *Glans resurfacing*
Three studies have reported results with glans resurfacing [82, 99, 100] 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, the rates of local recurrence were 0% [99] and 6% [100], without reports of nodal recurrence. There were no reported complications.

6.1.3.4   Glansectomy

Results of another fairly new technique, glansectomy, was reported in three studies [83, 101, 102], whilst a fourth study also reported on glans-preserving surgery [102]. A total of 68 patients with a follow-up of 114 months [101] and 63 months [102] were included. One patient (8%) had a local recurrence [101] and six patients (9%) had inguinal nodal metastases. No cancer-specific deaths were reported. Another group reported 87 patients with six local (6.9%), 11 regional (12.6%) and two systemic recurrences (2.3%), during a mean follow-up of 42 months [83].

6.1.3.5   Partial penectomy

Results of partial penectomy were reported in eight rather heterogeneous studies [87, 102-108] with 184 patients, with T1-T3 tumours, and follow-up from 40-194 months. Cancer specific mortality ranged from 0-27%, with local recurrence rates ranging from 4-50%. The 5-year OS rate was reported by three of the studies and ranged from 59-89% [105, 106, 108].

6.1.3.6   Summary of results of surgical techniques

There is not sufficient 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 5-year disease-specific survival 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 [109-114] (LE: 2b). External radiotherapy is given with a minimum dose of 60 Gy combined with a brachytherapy boost or brachytherapy on its own [110, 112]. Radiotherapy results are best with penile brachytherapy with local control rates ranging from 70-90% [110, 112]. 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 [115]. The rates of local recurrence after radiotherapy are higher than after partial penectomy. With local failure after radiotherapy, salvage surgery can achieve local control [116]. 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 [117] (LE: 3). With brachytherapy, meatal stenosis occurs in > 40% of cases.

Table 6: Summary of reported complications and oncological outcomes of local treatments*

Treatment	Complications	Local recurrence	Nodal recurrence	Cancer-specific deaths	References
Nd:YAG laser	None reported	10-48%	21%	2-9%	[88-91]
CO$_2$-laser	Bleeding, meatal stenosis both < 1%	14-23%	2-4%	None reported	[85-87]
Lasers (unspecified)	Bleeding 8%, local infection 2%	11-26%	2%	2-3%	[93-96]
Moh's micrographic surgery	Local infection 3%, Meatal stenosis 6%	32%	8%	3-4%	[97, 98]
Glans resurfacing	None reported	4-6%	Not reported	Not reported	[82, 99, 100]
Glansectomy	None reported	8%	9%	None reported	[101, 102]
Partial penectomy	Not reported	4-13%	14-19%	11-27%	[87, 105, 106, 108]
Brachytherapy	Meatal stenosis > 40%	10-30%	Not reported	Not reported	[109, 110, 112]
Radiotherapy	Urethral stenosis 20-35%, Glans necrosis 10-20%	Not reported	Not reported	Not reported	[111, 114-117]

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 [103] (LE: 3; GR: C). Radiotherapy is an option (see Section 6.1.6). Partial amputation should be considered in patients unfit for reconstructive surgery [116] (GR: C).

6.1.5.2   Treatment of disease invading the corpora cavernosa and/or urethra (T2/T3)
Partial amputation with a tumour-free margin with reconstruction is standard [113] (GR: C). A surgical margin of 5 mm is considered safe [83, 84]. 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%) [84]. Total penectomy with perineal urethrostomy is standard surgical treatment for T3 tumours [84] (GR: C).

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) (GR: C). Otherwise, adjuvant chemotherapy or palliative radiotherapy are options (GR: C; 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 [61, 81, 84, 113] (GR: C). For large or high-stage recurrence, partial or total amputation is required [117] (GR: C). A total phallic reconstruction may be offered to patients undergoing total/subtotal amputation [118, 119].

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 CO_2 or 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.		

CO_2 = carbon dioxide; Nd:YAG = neodymium:yttrium-aluminium-garnet.

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 [79].

All inguinal sentinel nodes appear to be located in the superior and central inguinal zones, with most in the medial superior zone [80]. No lymphatic drainage was observed from the penis to the two inferior regions of the groin and no direct drainage to the pelvic nodes was visualised. These findings confirm earlier studies [81, 82].

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 paracaval 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 (GR: B). 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 extranodal 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 [83]. 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) [84] 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 [85, 86]. One prospective study comparing bilateral lymphadenectomy, radiotherapy and surveillance in clinically node-negative patients reported that 5-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) [87].

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 [88, 89]. This risk must be taken into account when considering surveillance and the patient informed. Surveillance can only be recommended in patients with pTis and pTa penile cancer and with the appropriate caveats in pT1G1 tumours [88-90]. 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 [91]. Nomograms are unreliable in predicting node involvement [88, 92, 93] (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 [86, 94] (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 [79, 95] (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 (Tc99m) 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 [96] (GR: B). DSNB has a reported high sensitivity (90-94%) [96, 97] (LE: 2b). In a pooled meta-analysis of 18 studies, pooled sensitivity was 88%, which improved to 90% with the addition of patent blue [98].

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 [85]. The false-negative rate may be as high as 12-15% for DSNB, even in experienced centres [89, 90]. 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 [120].

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-FDGPET/CT can identify additional metastases in lymph-node positive patients [121]. Dynamic sentinel node biopsy (DSNB) is not reliable in patients with palpably enlarged and suspicious inguinal lymph nodes and should not be used [122] (LE: 3).

6.2.2.1 *Radical inguinal lymphadenectomy*

In clinically lymph node positive patients, surgical staging by inguinal lymphadenectomy is indicated. Intraoperative frozen sections may be used to confirm lymph node metastasis, for which an ipsilateral radical inguinal lymphadenectomy is necessary [79, 84].

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% [123] in the presence of significant risk factors such as increased body mass index. However, recent series have reported lower morbidities of about 25% [124, 125] (LE: 2b). Therapeutic radical inguinal lymphadenectomy can be life-saving and should not be underused for fear of associated morbidity [126]. Lymph node density is a prognostic factor [127].

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 [128, 129]. Post-operative morbidity is reduced by additional measures to improve drainage, such as stockings, bandaging, inguinal pressure dressings or vacuum suction [130] 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 lymphocoele formation (2.1-4%) [124, 125].

Laparoscopic and robot-assisted inguinal lymphadenectomy is feasible, but may not provide any advantage [131-134].

6.2.2.2 *Pelvic lymphadenectomy*

Patients with positive pelvic nodes have a worse prognosis compared to patients with only inguinal nodal metastasis (5-year CSS 71.0% vs. 33.2%) [135]. 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 3), the diameter of inguinal metastatic nodes (cut-off 30 mm) and extranodal extension. The percentage of pelvic nodal metastases was 0% without any of these risk factors and 57.1% with all three risk factors [135].

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 [136] 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 [84, 137] (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 [138].

6.2.2.3   Adjuvant treatment

In patients with pN2/pN3 disease, adjuvant chemotherapy is recommended [139] (GR: C) (see Section 6.3.1). This is because a retrospective study reported long-term disease-free survival of 84% in node-positive patients with adjuvant chemotherapy after radical lymph node surgery vs. 39% in historical controls without chemotherapy after lymphadenectomy [139].

Although adjuvant radiotherapy has been used after inguinal lymphadenectomy, the data is 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 (GR: B) as it is non-curative and usually destructive. Multimodal treatment with neoadjuvant chemotherapy followed by radical lymphadenectomy in clinically responsive cases is recommended [140-142]. Responders to neoadjuvant chemotherapy with post-chemotherapy surgery have been reported to achieve long-term survival in 37% of cases [140]. 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 5-year CSS rate of 16% [143].

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 [144]. One prospective trial found that inguinal node dissection was superior to inguinal radiotherapy [145]. Another study reported poor long-term survival in patients with adjuvant inguinal and pelvic radiotherapy [146]. Adjuvant chemotherapy has been reported to be far superior to adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive patients in one retrospective series [139]. 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' [147].

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.

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 DSNB.	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.		

DSNB = dynamic sentinel node biopsy.

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 [140, 148-151]. 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 disease-free survival (DFS) of 84% in 25 consecutive patients treated with 12 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% [140].

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-FU which they had been using since 1991 with lower toxicity and even better results compared to VBM [150] (LE: 2b). The same group has been using an adjuvant taxane-based regimen since 2004, cisplatin, 5-fuorouracil (5-FU) plus paclitaxel or docetaxel (TPF), in 19 node-positive patients receiving 3-4 cycles of TPF after resection of pN2-3 disease [151]. 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 [152].

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 5-20 patients treated with bleomycin-vincristine-methotrexate (BVM) and bleomycin-methotrexate-cisplatin (BMP) treatments [141, 142, 153] and in the confirmatory BMP trial of the Southwest Oncology Group [154]. 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 [155, 156]. Over a period of 30 years, five different neoadjuvant chemotherapy regimens were used in 20 patients [79], 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) [157].

A phase II trial evaluated treatment with four cycles of neoadjuvant paclitaxel, cisplatin, and ifosfamide (TIP). An objective response was reported in 15/30 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 [158] (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 [151]. 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 [159] (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; GR: B).

There are hardly any data concerning radiochemotherapy with lymph-node surgery in penile cancer. Radiochemotherapy should only be offered in clinical trials [160].

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 > 1 were independent prognostic factors, and that cisplatin-based regimens had better outcomes than non-cisplatin-based regimens after adjusting for prognostic factors [161] (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 [157]). 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 [79, 141, 142, 152-159, 162].

There is 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 [163] (LE: 2a; GR: B). Anecdotally, a benefit has been observed by combining cisplatin with gemcitabine [164] (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 [165-168]. 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 [165, 166] 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 [168]. Further clinical studies are needed (LE: 4).

6.3.6   *Guidelines for chemotherapy in penile cancer patients*

Recommendations	LE	GR
Treat with adjuvant chemotherapy (3-4 cycles of TPF) in patients with pN2-3 tumours.	2b	C
Treat with neoadjuvant chemotherapy (4 cycles of a cisplatin and taxane-based regimen) followed by radical surgery in patients with non-resectable or recurrent lymph node metastases.	2a	B
In patients with systemic disease and a limited metastatic load, treat with chemotherapy.	3	C

TPF = cisplatin, 5-fluorouracil, paclitaxel

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 disease-specific survival. Follow-up is also important in the detection and management of treatment-related complications.

Local or regional nodal recurrences usually occur within 2 years of primary treatment [79]. After 5 years, all recurrences were either local recurrences or new primary lesions [79]. These results support an intensive follow-up regimen during the first 2 years, with a less intensive follow-up after this for a total of at least 5 years. Follow-up after 5 years may be omitted in motivated patients reliably able to continue to carry out regular self-examination [79].

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 3-monthly intervals for the first 2 years so patients can benefit from adjuvant chemotherapy.

Although rarely late local recurrences may still occur, life-threatening metastases become very unusual after 5 years. This means regular follow-up can be stopped after 5 years, provided the patient understands the need to report any local changes immediately [169]. 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 [79, 170]. Local recurrence occurred during the first 2 years in up to 27% of patients treated with penis-preserving modalities [171]. After partial penectomy, the risk of local recurrence is about 4-5% [79, 170, 171].

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 2 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 2 years. It is therefore wise to continue close follow-up in these patients, for whom self-examination is very important [172]. 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 [67, 172, 173]. 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% [79]. 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 1-2	Years 3-5			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	3 months	6 months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for CIS.	5 years	C
Amputation	3 months	1 year	Regular physician or self-examination.	5 years	C
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	3 months	6 months	Regular physician or self-examination.	5 years	C
pN0 at initial treatment	3 months	1 year	Regular physician or self-examination. Ultrasound with FNAB optional.	5 years	C
pN+ at initial treatment	3 months	6 months	Regular physician or self-examination. Ultrasound with FNAC optional, CT/MRI optional.	5 years	C

CIS = carcinoma in situ; CT = computed tomography; FNAB = fine-needle aspiration biopsy;
FNAC = fine-needle aspiration cytology; MRI = magnetic resonance imaging.

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 [174]. 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 [93] in 58/67 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 lifes, similar to that of the general Swedish population.
        A large study on CO_2 laser treatment of penile cancer in 224 patients reported no problems with erectile capability or sexual function following treatment [85]. In another study [96], no sexual dysfunction occurred in 19 patients treated.

7.2.3   Sexual activity after glans resurfacing
In one study with 10 patients [99], 7/10 completed questionnaires (International Index of Erectile Function [IIEF-5] and a non-validated 9-item questionnaire) at their 6-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 3-5 months. According to the (non-validated) questionnaire, 7/7 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 2-3 weeks of surgery. Six out of seven patients had had sexual intercourse within 3 months of surgery and 5/7 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 [101], 79% did not report any decline in spontaneous erection, rigidity and penetrative capacity after surgery, while 75% reported recovery of orgasm. In another study [102], all 12 patients had returned to 'normal' sexual activity 1 month after surgery.

7.2.5 **Sexual function after partial penectomy**

Sexual function after partial penectomy was reported by three studies [175-177]. The IIEF questionnaire was used in 18 patients with a mean age of 52 years [175]. 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 14/18 patients with a median time since surgery of 11.5 months (range 6-72) [176]. Prior to surgery, all patients had normal erectile function and intercourse at least once a month. In 9/14 patients, sexual functioning was 'normal' or 'slightly decreased', while 3/14 patients had no sexual intercourse after surgery. Alei *et al.* showed an improvement in erectile function over time [177].

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 [176]. 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 [118, 178, 179] 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 [48] 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.

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9.   CONFLICT OF INTEREST

EAU Guidelines on

Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)

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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.

1.2   Panel composition
The EAU Non-neurogenic Male LUTS Guidelines Panel consists of an international group of experts with urological and 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 2016 document presents a comprehensive update of the 2015 publication. The literature was assessed for all chapters.

2.   METHODS

2.1   Introduction
For the 2016 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 only (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 January 1st 2014 and May 31st 2015. A total of 1172 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.

In addition, specific sections of the Guideline were updated by way of systematic review 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 2016 Management of Non-Neurogenic Male LUTS Guidelines update are:
1.   What is the diagnostic performance of non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS compared with pressure-flow studies [1]?

2.   What is the best treatment for nocturia or nocturnal incontinence in terms of improving symptom
        severity and quality of life?

For Chapter 4 (Diagnostic evaluation), the Panel used the Delphi technique consensus approach [2], facilitated by bespoke software (www.acord.it). Based on consensus findings the Panel classified diagnostic tests into three categories: 'must', 'should', and 'may'. 'Must' presents the highest level of obligation, 'Should' presents an intermediate level, and 'May' expresses the lowest level of obligation.

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 [3]. 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 all Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2   Review
Guideline sections resulting from the systematic reviews have been peer-reviewed. The remainder of the text was reviewed 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   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 (www.uroweb.org/guidelines/).

3.   EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

LUTS can be divided into storage, voiding and post-micturition symptoms [4]. LUTS are prevalent, cause bother and impair QoL [5-8]. Increasing awareness of LUTS and storage symptoms in particular, is warranted to discuss management options that could increase QoL [9]. LUTS are strongly associated with ageing [5, 6], associated costs and burden are therefore likely to increase with future demographic changes [6, 10]. LUTS are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g. metabolic syndrome) [11]. Most elderly men have at least one LUTS [6]. However, symptoms are often mild or not very bothersome [8, 9, 12]. LUTS progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [6]. 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 [4, 7]. Recent studies have shown, however, that LUTS are often unrelated to the prostate [6, 13]. Bladder dysfunction may also cause LUTS, including detrusor over-activity/OAB, detrusor underactivity/underactive bladder, as well as other structural or functional abnormalities of the urinary tract and its surrounding tissues [13]. In addition, many non-urological conditions also contribute to LUTS, especially nocturia [6].

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 [4].
*   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 [4].
*   Bladder outlet obstruction (BOO) 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 flowrate and detrusor pressure [4].
*   Benign prostatic obstruction (BPO) is a form of BOO and may be diagnosed when the cause of outlet

obstruction is known to be BPE [4]. In our Guidelines we use either the term BPO or BOO as reported by the original studies.
- Benign prostatic hyperplasia (BPH) 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 [4].
- Overactive bladder syndrome (OAB) 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)
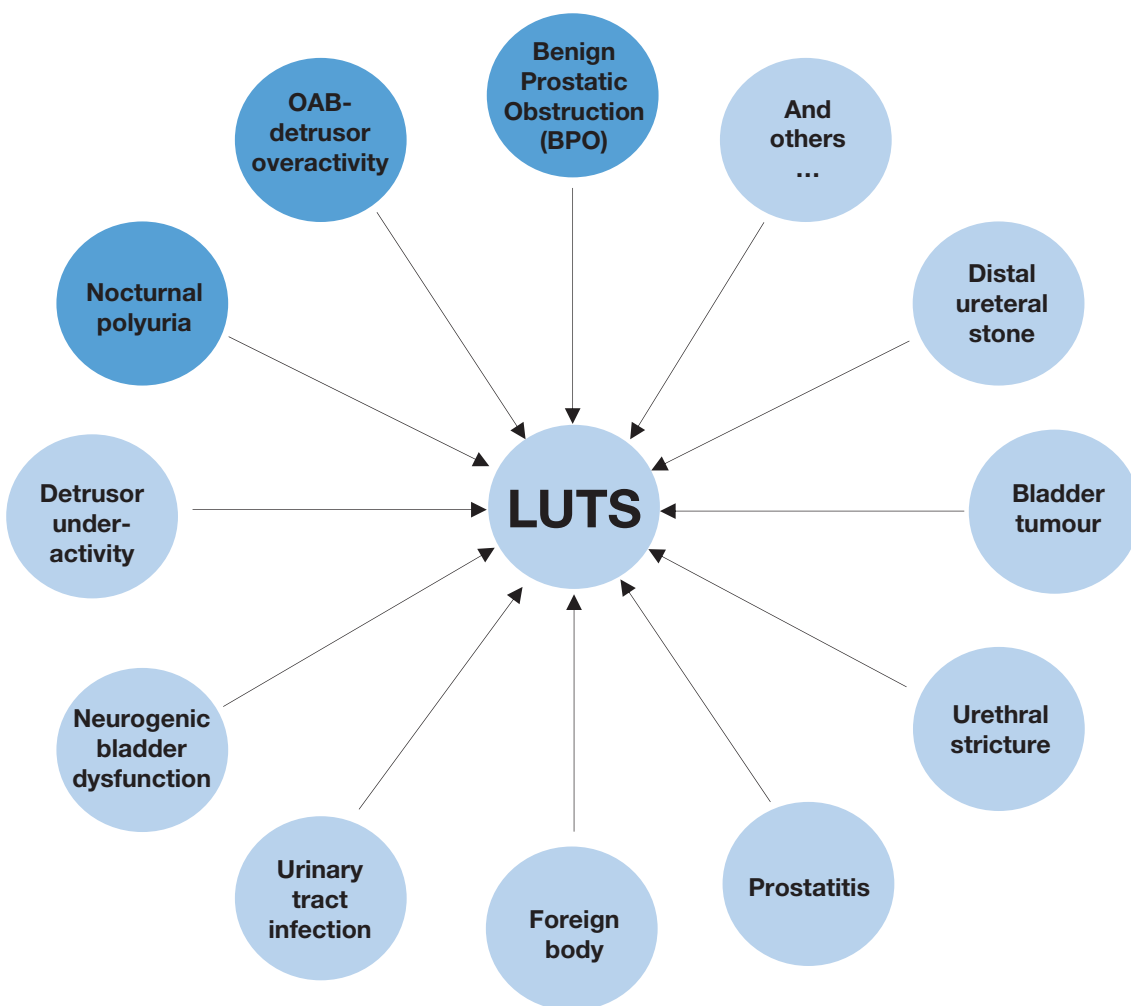
4. DIAGNOSTIC EVALUATION

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 investigated, preferably with validated symptom questionnaires such as the International Index for Erectile Function (IIEF).

Recommendation	LE	GR
A medical history must be taken from men with LUTS.	4	A*

Upgraded based on Panel consensus. LUTS = lower urinary tract symptoms.

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, of post-micturition symptoms, and of 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
A validated symptom score questionnaire including QoL assessment should be used during the assessment of male LUTS and for re-evaluation during and/or after treatment.	3	B

LUTS = lower urinary tract symptoms; QoL = quality of life.

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 [4]. Parameters that can be derived from the FVC bladder diary include: daytime and night-time voiding frequency, total voided volume, the fraction of urine production during the night (nocturnal polyuria index [NPi]), 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
Micturition frequency volume charts or bladder diaries should be used to assess male LUTS with a prominent storage component or nocturia.	3	B
Frequency volume charts should be performed for the duration of at least three days.	2b	B

LUTS = lower urinary tract symptoms.

4.4 Physical examination and digital-rectal examination

Physical examination to seek potential influences on LUTS, particularly focussing 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
Physical examination including DRE should be a routine part of the assessment of male LUTS.	3	B

DRE = digital-rectal examination; LUTS = lower urinary tract symptoms.

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
Urinalysis (by dipstick or urinary sediment) must be used in the assessment of male LUTS.	3	A*

Upgraded based on Panel consensus. LUTS = lower urinary tract symptoms.

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 (± 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 positive predictive value of PSA for the detection of BPO was recently shown to be 68% [59]. In an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [60].

Recommendation	LE	GR
PSA measurement should be performed only if a diagnosis of PCa will change the management or if PSA can assist in decision-making in patients at risk of progression of BPE.	1b	A

BPE = benign prostate enlargement; PCa = prostate cancer; PSA = prostate-specific antigen.

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
Renal function assessment must be performed 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. LUTS = lower urinary tract symptoms.

4.8   Post-void residual urine
Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation. PVR 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% to 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 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 α1-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
Measurement of PVR in male LUTS should be a routine part of the assessment.	3	B

LUTS = lower urinary tract symptoms; PVR = post-void residual.

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. Q_{max} is prone to within-subject variation [73, 74]; it is therefore 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 underfilled bladder [77]. Thus, it is limited as a diagnostic test because 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

LUTS = lower urinary tract symptoms.

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). US allows for a 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, lower radiation dose and less side-effects [79].

Recommendation	LE	GR
Imaging of the upper urinary tract (with US) in men with LUTS should be performed in patients with a large PVR, haematuria or a history of urolithiasis.	3	B

LUTS = lower urinary tract symptoms; PVR = post-void residual; US= ultrasound.

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 5α-reductase inhibitors (5-ARIs). Prostate volume predicts symptom progression and the risk of complications [81].

TRUS 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
When considering medical treatment for male LUTS, imaging of the prostate (either by TRUS or transabdominal US) should be performed if it assists in the choice of the appropriate drug.	3	B
When considering surgical treatment, imaging of the prostate (either by TRUS or transabdominal US) should be performed.	3	B

LUTS = lower urinary tract symptoms; TRUS = transrectal ultrasound; US = ultrasound.

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 an 'obstructive' 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
Urethrocystoscopy should be performed 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

LUTS = lower urinary tract symptoms.

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*
PFS are the basis for the definition of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. BOO/BPO has to be differentiated from DUA, which signifies decreased detrusor pressure during voiding in combination with decreased urinary flow rate [4].

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.

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 the 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 [93].

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
PFS should be performed only in individual patients for specific indications prior to invasive treatment or when evaluation of the underlying pathophysiology of LUTS is warranted.	3	B
PFS should be performed in men who have had previous unsuccessful (invasive) treatment for LUTS.	3	B
When considering invasive treatment, PFS may be used for patients who cannot void > 150 mL.	3	C
When considering invasive therapy in men with bothersome, predominantly voiding LUTS, PFS may be performed in men with a PVR > 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, PFS should be performed in men aged < 50 years.	3	B

LUTS = lower urinary tract symptoms; PFS = pressure-flow studies, PVR = post-void residual.

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) [94]. PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward 1 as the prostate becomes more circular. PCAR sensitivity was 77% for diagnosing BPO when PCAR was > 0.8, with 75% specificity [94].

US 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.

IPP correlates well with BPO (presence and severity) on urodynamic testing, with a PPV of 94% and a NPV of 79% [95]. IPP may correlate with prostate volume, DO, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [96]. IPP also seems to predict successfully the outcome of a trial without catheter (TWOC) after AUR [97, 98]. No information with regard to intra- or inter-observer variability and learning curve is yet available. IPP may be a feasible option to infer BPO in men with LUTS. The role of IPP as a non-invasive alternative to pressure flow studies (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 [99].

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 [100]. DWT 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 [101].

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 [102]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [103]. 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 [104, 105]. Severe LUTS and a high UEBW (≥ 35 g) are risk factors for prostate/BPH surgery in men on α-blockers [106].

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 [107] and interobserver agreement [108], and a nomogram has been derived [109]. A method in which flow is not interrupted is also under investigation [110].

The data generated with the external condom method [111] correlates with invasive PFS in a high proportion of patients [112]. Resistive index [113] and prostatic urethral angle [114] 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 pressure-flow studies has been investigated by a systematic review performed by the Panel [1].

A total of 40 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, Intravesical prostate protrusion, Doppler US, Prostate volume/height, and Near-infrared spectroscopy. Overall, 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, positive predictive value and negative predictive value of the non-invasive tests were highly variable.

Recommendation	LE	GR
None of the non-invasive tests in diagnosing BOO in men with LUTS can currently be recommended as an alternative for pressure-flow studies.	1a	B

LUTS = lower urinary tract symptoms; BOO = bladder outlet obstruction.

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.

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┌─────────────────┐                                    ┌──────────────────────┐
│   Male LUTS     │                                    │ Manage according to  │
└────────┬────────┘                                    │     EAU mLUTS        │
         │                                             │  treatment algorithm │
         ▼                                             └──────────▲───────────┘
┌─────────────────────────────────────┐                          │
│   History (+ sexual function)       │                     ┌────┴────┐
│   Symptom score questionnaire       │                     │   No    │
│   Urinalysis                        │                     └────▲────┘
│   Physical examination              │                          │
│   PSA (if diagnosis of PCa will     │───────┐         ┌────────┴─────────┐
│   change the management –           │       └────────▶│   Bothersome     │
│   discuss with patient)             │                 │    symptoms      │
│   Measurement of PVR                │                 └────────┬─────────┘
└──┬──────────────────────┬───────────┘                          │
   │                      │                                 ┌─────┴─────┐
   │                      │                                 │    Yes    │
   ▼                      ▼                                 └─────┬─────┘
┌──────────────┐   ┌──────────────┐                              │
│ Abnormal DRE │   │Significant PVR│                   ┌─────────▼──────────────┐
│ Suspicion of │   └──────┬───────┘                   │ FVC in cases of        │
│ neurological │          │                           │ predominant storage    │
│   disease    │          ▼                           │ LUTS/nocturia          │
│  High PSA    │   ┌──────────────┐                    │ US assessment of       │
│  Abnormal    │   │US of kidneys │───────────────────▶│ prostate               │
│  urinalysis  │   │+/- Renal     │                    │ Uroflowmetry           │
└──────┬───────┘   │ function     │                    └─────────┬──────────────┘
       │           │ assessment   │                              │
       ▼           └──────────────┘                              ▼
┌──────────────┐                            ┌──────────────┐  ┌──────────────────────┐
│ Evaluate     │                            │Medical       │  │ Benign conditions of │
│ according to │                            │treatment     │◀─│ bladder and/or       │
│ relevant     │                            │according to  │  │ prostate with        │
│ guidelines   │                            │treatment     │  │ baseline values      │
│ or clinical  │                            │algorithm     │  │ PLAN TREATMENT       │
│ standard     │                            └──────────────┘  └──────────────────────┘
└──────┬───────┘
       │           ┌─────────────────────────────┐
       ▼           │ Endoscopy (if test would     │
┌──────────────┐   │ alter the choice of surgical │
│ Treat        │   │ modality)                    │──────────┐
│ underlying   │   │ Pressure flow studies        │          │
│ condition    │   │ (see text for specific       │          │
│ (if any,     │   │ indications)                 │          ▼
│ otherwise    │   └──────────────────────────────┘  ┌──────────────────────┐
│ return to    │                                     │ Surgical treatment   │
│ initial      │                                     │ according to         │
│ assessment)  │                                     │ treatment algorithm  │
└──────────────┘                                     └──────────────────────┘
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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. WW 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) [115, 116], whilst others can remain stable for years [117]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [118].

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 [119, 120]. 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 [117, 118, 121, 122] 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 [121, 122] (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 [121].

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 [123]. 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

LUTS = lower urinary tract symptoms.

5.2 Pharmacological management

5.2.1 α1-Adrenoceptor antagonists (α1-blockers)

Mechanism of action: α1-blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO [124]. However, α1-blockers have little effect on urodynamically determined bladder outlet resistance [125], and treatment-associated improvement of LUTS is correlated only poorly with obstruction [126]. Thus, other mechanisms of action may be relevant.

α1-adrenoceptors located outside the prostate (e.g. urinary bladder and/or spinal cord) and α1-adrenoceptor subtypes (α1B- or α1D-adrenoceptors) may play a role as mediators of effects. α1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events.

α1-blockers currently available are: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin). α1-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 α1-blockers demonstrate that all α1-blockers have a similar efficacy in appropriate doses [127]. Effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [128].

Controlled studies show that α1-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, 128]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [55, 128].

α1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of < 1 year, but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [56, 129-132]. α1-blocker efficacy is similar across age groups [128]. α1-blockers neither reduce prostate size nor prevent AUR in long-term studies [130-132]; some patients must therefore be treated surgically. Nevertheless, IPSS reduction and Q_{max} improvement during α1-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 α1-blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin, and are less common for alfuzosin and tamsulosin [133]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α1-blocker-induced vasodilatation [134]. In contrast, the frequency of hypotension with the α1A- selective blocker silodosin is comparable with placebo [135].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [136]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers [137]. However, the odds-ratio for IFIS was much higher for tamsulosin. It appears prudent not to initiate α1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α1-blocker use.

A systematic review concluded that α1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation [138]. 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, doxazosin and terazosin were associated with a risk similar to placebo. Tamsulosin was associated with a lower risk of ejaculatory dysfunction (EjD) than silodosin (OR:0.09; p <0.00001). 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 α1-blocker is the greater the incidence of EjD.

Practical considerations: α1-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, α1-blockers do not prevent incidence of urinary retention or need for surgery. Ophthalmologists should be informed about α1-blocker use prior to cataract surgery. Patients should be counselled on the risk of EjD caused by α1-blockers.

Recommendation	LE	GR
Offer α1-blockers to men with moderate-to-severe LUTS.	1a	A

LUTS = lower urinary tract symptoms.

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 [139]. 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 [140] leading to prostate size reduction of about 18-28% and a decrease in circulating PSA levels of about 50% after 6-12 months of treatment [141]. 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 6-12 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, 130, 131, 142-148]. Indirect comparison and one direct comparative trial (12 months duration) indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [141, 149]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [150]. 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 [151, 152]. 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 α1-blocker tamsulosin [130, 148, 153]. 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 α1-blockers, reduce the long-term (> 1 year) risk of AUR or need for surgery [56, 146, 154]. In the Proscar Long-Term Efficacy and Safety Study, finasteride treatment reduced the relative risk of AUR by 57%, and surgery by 55% at four years, compared with placebo [146]. 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 [155]. 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 [156, 157].

Finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation [158].

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, 131, 141]. 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 [159, 160]. Although no causal relationship with high-grade PCa has been proven, men taking a 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 [161]. In a 5 years 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) [161].

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). 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 for PCa screening.

Recommendations	LE	GR
Offer 5α-reductase inhibitors to men who have moderate-to-severe LUTS and an enlarged prostate (> 40 mL).	1b	A
5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and the need for surgery.	1b	A

LUTS = lower urinary tract symptoms.

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 [162, 163]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [164, 165].

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 [166, 167].

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 that assumption [168]. A sub-analysis of an open-label trial of OAB patients showed that age but not gender has an impact on urgency, frequency, or urgency incontinence [169].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO has been tested (online supplementary Table S.18) [170-176]. Most trials lasted only 12 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 [171, 173, 176, 177]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency, urgency-related voiding and improved 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 [172, 175].

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 [174].

A further analysis showed that men with PSA levels of < 1.3 ng/mL (smaller prostates) might profit more from antimuscarinic drugs [178]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [175, 179]. In a small RCT without placebo, propiverine improved frequency and urgency episodes [179]. In an open-label study, tolterodine decreased 24-hour micturition, nocturia and American Urological Association Symptom Index scores [175].

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 or urinary retention. A 12-week safety study on men with mild to moderate BOO showed that tolterodine increased the PVR (49 mL vs. 16 mL) but not AUR (3% in both arms) [180]. 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 [180].

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 after initiation of therapy is noted.

Recommendations	LE	GR
Muscarinic receptor antagonists may be used in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	1b	B
Caution is advised in men with a PVR volume greater than 150 mL.	4	C

LUTS = lower urinary tract symptoms; PVR = post-void residual.

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 [181]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the LUT [182]. Finally, PDE5Is could reduce chronic inflammation in the prostate and bladder [183]. 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} [184].

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 [185]; the maximum trial (open label) duration was 52 weeks [186]. 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 [187]. Among sexually active men > 45 years with comorbid LUTS/BPH and ED, tadalafil improved both conditions [188].

An integrated data analyses from 4 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 [189]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [190].

The combination of PDE5Is and α-blockers has also been evaluated. A meta-analysis of 5 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 [184]. The effects of tadalafil 5 mg combined with finasteride 5 mg were assessed in a recent 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 [191]. 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 [184]. Discontinuation rate due to adverse effects for tadalafil was 2.0% [192] and did not differ by age, LUTS severity, testosterone levels, or prostate volume in the pooled data analyses [187].

PDE5Is are contraindicated in patients using nitrates, the potassium channel opener nicorandil, or the α1-blockers doxazosin and terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (< 3 months) or stroke (< 6 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 profit the most from treatment with PDE5Is [184].

Long-term experience with tadalafil in men with LUTS is limited to one trial with 1-year follow-up [186], and therefore conclusions about its efficacy or tolerability > 1 year are not possible. There is limited information on reduction of prostate size and no data on disease progression.

Recommendations	LE	GR
PDE5Is may be used in men with moderate-to-severe LUTS with or without erectile dysfunction.	1a	A

LUTS = lower urinary tract symptoms; PDE5Is = phosphodiesterase type 5 inhibitors.

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 to 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, ß-sitosterol, fatty acids, and lectins [193]. *In vitro*, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects; decrease sexual hormone binding globulin; inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostatic cells, α-adrenoceptors, 5 α-reductase, muscarinic cholinoceptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [193-195]. 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 [196]. In addition, batches from the same producer may contain different concentrations of active ingredients [197]. 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 in active principles [198]. 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. Analysis of each drug class can also be found in the supplementary online material (http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/).
      Cochrane meta-analyses suggest that a) men treated with *Pygeum africanum* were twice as likely to report symptom improvement, b) men treated with *Secale cereale* were twice as likely to benefit from therapy compared to placebo and c) *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) [199-201].
      Recently, short-term studies on the combination of plant extracts with tamsulosin have been published with promising results [202, 203]. The combination treatment with *Serenoa Repens*, Lycopene (Ly), and 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 12 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 study medication. Gastrointestinal complaints were the most commonly reported. In formulations with *Hypoxis rooperi*, ED appeared in 0.5% of patients.

Practical considerations: Phytotherapeutic agents are a heterogeneous group and may contain differing concentrations of the 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 because of product heterogeneity, 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 three 12-week RCTs conducted in Europe, Australia, and North America and a further 12-month randomised, double-blind, active treatment-controlled study in OAB patients [204-207]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency incontinence, urgency and also patient perception of treatment benefit.

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [204-207]. 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 [204]. 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 [208]. Overall change in PVR with mirabegron is small [208].

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 [209]. One small study has looked at change in symptom scores in men receiving mirabegron with tamsulosin 0.2 mg daily [210].

Recommendation	LE	GR
Beta-3 agonists may be used in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms.	1b	B

LUTS = lower urinary tract symptoms.

5.2.7 Combination therapies
5.2.7.1 α1-blockers + 5α-reductase inhibitors
Mechanism of action: Combination therapy consists of an α1-blocker (Section 5.2.1) together with a 5-ARI (Section 5.2.2). The α1-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 α1-blocker, 5-ARI or placebo alone (online supplementary Table S.21). Initial studies with follow-up periods of 6-12 months demonstrated that the α1-blocker was superior to finasteride in symptom reduction, whereas combination was not superior to α1-blocker monotherapy [143, 144, 211]. In studies with a placebo arm, the α1-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 (4 years) from MTOPS, and Combination of Avodart and Tamsulosin (CombAT) showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α-blocker in reducing the risk of AUR or need for surgery [56, 130, 131].

The CombAT study demonstrated that combination treatment is superior to either monotherapy regarding symptoms and flow rate starting from month nine, and superior to α1-blocker for AUR and the need for surgery after eight months [131]. Thus the differences in MTOPS may reflect different inclusion and exclusion criteria and baseline patient characteristics.

Discontinuation of the α1-blocker after 6-9 months of combination therapy was investigated by an RCT and an open-label multicentre trial [212, 213]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [212], 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 [213]. LUTS improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.44). However, the limitations of the studies include the short duration and the short follow-up period after discontinuation.

In both the MTOPS and CombAT trials, 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 [214]. To prevent one case of urinary retention and/or surgical treatment 13 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 2-years 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) [215]. Furthermore, tamsulosin plus dutasteride significantly reduced the relative risk of clinical progression (mainly characterised as worsening in symptoms) by 43.1% when compared with WW, all, with an absolute risk reduction of 11.3% (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 4-year results of the CombAT study. Combination therapy provided consistent improvement of LUTS over tamsulosin across all analysed baseline variables at 48 months [216].

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 [191].

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [56, 130, 131]. The adverse events observed during combination treatment were typical of α1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy.

Practical considerations: Compared with α1-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 12 months) is intended and patients should be informed about this. Discontinuation of the α1-blocker after six months might be considered in men with moderate LUTS.

Recommendation	LE	GR
Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and risk of disease progression (e.g. prostate volume > 40 mL).	1b	A

LUTS = lower urinary tract symptoms.

5.2.7.2 α1-blockers + muscarinic receptor antagonists
Mechanism of action: Combination treatment consists of an α1-blocker together with an antimuscarinic aiming to antagonise both α1-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 4-12 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 α1-blocker [174, 175, 214, 217-223] (online supplementary Table S.22). One trial used the α1-blocker naftopidil (not registered in most European countries) with and without antimuscarinics

[224]. A high proportion of men with voiding and storage LUTS need to add anticholinergics after α1-blocker monotherapy, particularly those with longer duration of symptoms at presentation, and men with storage symptoms and a small prostate volume [225].

Combination treatment is more efficacious in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone, and improves QoL [174]. 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 [178].

Persistent LUTS during α1-blocker treatment can be reduced by the additional use of an antimuscarinic, especially when DO is demonstrated [175, 214, 217, 223]. Two systematic reviews of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [226, 227]. Effectiveness of therapy is evident primarily in those men with moderate-to-severe storage LUTS [228]. 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 [229]. 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 α1-blocker monotherapy [230].

Tolerability and safety: Adverse events of both drug classes are seen with combined treatment using α1-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 [226, 227].

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 [231]. The combination therapy was not inferior to placebo for the primary urodynamic variables; Q_{max} was increased versus placebo [231].

Practical considerations: Class effects are likely to underlie efficacy and QoL using an α1-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 α1-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 PVR volume > 150 mL.	2b	B

LUTS = lower urinary tract symptoms; PVR = post-void residual.

5.3 Surgical treatment

5.3.1 *Transurethral resection of the prostate and transurethral incision of the prostate*

Mechanism of action: TURP 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 5 years, TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [232]. 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 [233]. One study with a mean follow-up of 13 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.23 presents RCTs comparing TUIP with TURP [234-241]. A meta-analysis of short- and long-term data from 10 RCTs found similar LUTS improvements and lower but insignificant improvements in Q_{max} for TUIP [236]. 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 re-treatment rate of 2.6% after a mean follow-up of 16 months [242]. In a large-scale study of 20,671 men, the overall re-treatment rates (re-TURP, urethrotomy and bladder neck incision) were 5.8%, 12.3%, and 14.7%, at 1, 5, and 8 years of follow-up, respectively, and the respective incidence of re-TURP was 2.9%, 5.8% and 7.4% [243]. A meta-analysis of six trials showed that

re-operation was more common after TUIP (18.4%) than after TURP (7.2%) [236].

Tolerability and safety: Peri-operative mortality and morbidity have decreased over time, but the latter remains considerable (0.1% and 11.1%, respectively) [244]. The possibility of increased long-term mortality compared to open surgery [245] has not been verified [246-248]. 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 1 year, 12.7% vs. 11.8% at 5 years, 20% vs. 20.9% at 8 years) and that the 8-year myocardial infarction rates were identical (4.8 vs. 4.9%) [243].

The risk of TUR-syndrome decreased to < 1.1% [242, 249]. No case has been recorded after TUIP. Data from 10,654 TURPs reported bleeding requiring transfusion in 2.9% [244]. The risk after TUIP is negligible [268]. 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%) [232]. 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) [242].

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 [244]. The upper limit for TURP is mostly 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 [250, 251].

Efficacy: B-TURP is the most widely and thoroughly investigated alternative to M-TURP. Results from > 40 RCTs [252] have been reported, of which around half have been pooled in RCT-based meta-analyses [232, 253-256]. Early pooled results concluded that no clinically relevant differences exist in short-term (up to 12 months) efficacy (IPSS, QoL score and Q_{max}) [254]. Subsequent meta-analyses supported these conclusions [232, 253, 255, 256], 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.24) [257-263].

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). 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 12 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) [254]. Subsequent meta-analyses supported these conclusions [232, 253, 255, 256]. However, trial quality was relatively poor and limited follow-up might cause under-reporting of late complications, such as urethral stricture/BNC [254]. Data from individual RCTs with a follow-up of 12-60 months showed no differences in urethral stricture/BNC rates (online supplementary Table S.24) [257-264]. Nevertheless, in a recent RCT, a significantly higher stricture (urethral stricture+BNC) rate was detected for the first time in the B-TURP arm [265]. 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 favoring 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 arms in those with prostate volume 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).

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 [266]. A comparative evaluation of the effects on overall sexual function, quantified with IIEF-15 showed no differences between B-TURP and M-TURP at 12 months of follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [267].

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 readmissions 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 [254]. The duration of improvements with B-TURP was documented in a number of RCTs with a follow-up of > 12 months. Mid-term results (up to 5 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
M-TURP is the current surgical standard procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO. M-TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments.	1a	A
The morbidity of M-TURP is higher than for drugs or other minimally invasive procedures.	1a	A
B-TURP achieves short- and mid-term results comparable with M-TURP.	1a	A
B-TURP has a more favourable peri-operative safety profile compared with M-TURP.	1a	A
TUIP is the surgical therapy of choice for men with prostate sizes < 30 mL, without a middle lobe, and bothersome moderate-to-severe LUTS secondary to BPO.	1a	A

BPO = benign prostatic obstruction; B-TURP = bipolar TURP; LUTS = lower urinary tract symptoms; M-TURP = monopolar TURP; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

5.3.2 Open prostatectomy

Mechanism of action: Open prostatectomy (OP) 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 [268-275]. OP 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% [268-270, 276, 277]. Efficacy is maintained for up to 6 years [278].

A recent RCT-based meta-analysis evaluated the overall efficacy of endoscopic enucleation of the prostate (EEP) vs. OP for treating patients with large glands [279]. Seven RCTs involving 735 patients were included. Three RCTs compared OP with HoLEP [268, 269, 271] and four RCTs compared OP with EEP using bipolar circuitry [272-274, 278]. OP was performed via a transvesical approach in all RCTs. At 3-, 6- and 12-month follow-up, there were no significant differences in IPSS, Q_{max}, QoL score and PVR between EEP and OP. It was concluded that EEP appears to be an effective minimally invasive option for treating large prostates.

Tolerability and safety: OP mortality has decreased significantly during the past two decades (< 0.25%) [277]. The estimated transfusion rate is about 7-14% [268, 276, 277, 279]. Long-term complications include transient urinary incontinence (up to 10%), BNC and urethral stricture (about 6%) [268-270, 279, 280].

A recent RCT-based meta-analysis evaluated the overall safety of EEP vs. OP for treating patients with large glands [279]. 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. IIEF-5 was significantly higher with EP at 12 months. EEP 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: OP 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.

Recommendations	LE	GR
OP or EEP such as holmium laser or bipolar enucleation are the first choice of surgical treatment in men with a substantially enlarged prostate (e.g. > 80 mL) and moderate-to-severe LUTS.	1a	A
OP has a high operative morbidity.	1b	A

EEP = endoscopic enucleation of the prostate; LUTS = lower urinary tract symptoms; OP = open prostatectomy.

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.26) [281]. Symptom score after TUMT decreased by 65% in 12 months, compared to 77% after TURP. TURP also achieved greater improvement in Q_{max} (119% vs. 70%) [281].

In one pooled analysis of three studies (two RCTs and one cohort study) with 12-month follow-up, responder rate was 85.3% for ProstaLund Feedback TUMT (PLFT) and 85.9% for TURP [282]. IPSS showed a subjective, non-inferior improvement with PLFT [282]. 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 [283-286]. In one study with longer follow-up, cumulative re-treatment risk at 5 years was estimated to be 42% for those without retention and 59% for those with retention at the baseline [287].

An RCT-based systematic review [281] (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 5-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 by 10% after TUMT and by 4.3% after TURP. 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 4-5 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 [281, 282, 288]. 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 re-treatment rates for urethral stricture/BNC were significantly smaller for TUMT [281].

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 [289].

Recommendations	LE	GR
TUMT achieves symptom improvement comparable with TURP, but TUMT is associated with decreased morbidity and lower flow improvements.	1a	A
Durability is in favour of TURP which has lower re-treatment rates compared to TUMT.	1a	A

TUMT = transurethral microwave therapy; TURP = transurethral resection of the prostate.

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 10 single-arm studies showed that TUNA™ achieved a 50% decrease in IPSS and a 70% improvement in Q_{max} at one year [290]. These findings are supported by a more recent meta-analysis of 35 studies (9 comparative, 26 non-comparative) [291]. TUNA™ significantly improved IPSS and Q_{max}, but compared to TURP these improvements were significantly lower at 12 months. Mean differences in TURP vs. TUNA™ were 4.7 for IPSS and 5.9 mL/s for Q_{max} [291].

Clinical studies on the impact of TUNA™ on BPO [292, 293] 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 [292].

The overall re-treatment rate after TUNA™ was 19% based on an analysis of 17 non-comparative studies [291]; a rate considerably higher than that seen with TURP.

Tolerability and safety: Transient urinary retention and storage LUTS are common weeks post-operatively [294, 295]. Generally, TUNA™ is associated with fewer adverse events compared to TURP, including mild haematuria, urinary infections, strictures, incontinence, ED, and ejaculation disorders [290].

Practical considerations: TUNA™ can be performed as a day-case procedure under local anaesthesia or sedation [294]. TUNA™ is not suitable for prostates > 75 mL or isolated bladder neck obstruction. In addition, TUNA™ cannot effectively treat prostatic middle lobes. There are concerns about the durability of the effects achieved by TUNA™.

Recommendations	LE	GR
TUNA™ is a minimally invasive alternative with decreased morbidity compared to TURP but with less efficacy.	1a	A
Durability is in favour of TURP with lower re-treatment rates compared to TUNA™.	1a	A

TUNA™ = transurethral needle ablation; TURP = transurethral resection of the prostate.

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 [296]. 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 6 or 12 months post operatively (online supplementary Table S.28) [297]. One RCT comparing TURP with HoLRP with a minimum follow-up of 4 years showed no difference in urodynamics after 48 months [298]. Three meta-analyses covering trials on HoLEP vs. TURP found that symptom improvement was comparable or superior with HoLEP (online supplementary Table S.28) [299-301]. 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 [302]. Another RCT on HoLAP and 80-W PVP showed comparable functional improvement within a median follow-up of 71 months [303].

RCTs indicate that HoLEP is as effective as OP for improving micturition in large prostates [268, 269], with similar re-operation rates after 5 years (5% vs. 6.7%, respectively) [268]. One RCT comparing HoLEP with TURP in a small number of patients who completed the 7-year follow-up found that the functional long-

term results of HoLEP were comparable with TURP [304]. A retrospective study of HoLEP with the longest follow-up (up to 10 years, mean 62 months) reported durable functional results with low re-operation rates [305].

Tolerability and safety: Dysuria is the most common post-operative complication [296, 299]. Compared to TURP, HoLRP has shorter catheterisation and hospitalisation times [297, 306]. Potency, continence, and major morbidity at 48 months were identical between HoLRP and TURP [298]. 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 [299-301]. 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 [268, 269].

HoLEP has been safely performed in patients using anticoagulant medications [307, 308]. In a study of 83 patients, blood transfusion was required in seven patients (8%) [309]. A retrospective study compared the safety results of HoLEP between 39 patients who were on anticoagulant therapy at the time of their surgery, and 37 controls [308]. No transfusions were required and bleeding complication rates were not significantly different [308]. Short-term studies showed that patients with urinary retention could be treated with HoLEP [310, 311].

The impact on erectile function and retrograde ejaculation is comparable between HoLEP and TURP/OP [269, 312]. 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 [307, 313].

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 is the 180W-XPS laser, but the majority of evidence is published with the former 80-W (KTP) or 120-W HPS (LBO) laser system. These three "Greenlight" laser systems differ not only in maximum power output, but more significantly in fibre design and the associated different energy tissue interaction.

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.28) [314]. No differences were found in Q_{max} and IPSS between 80-W-PVP and TURP, but only three RCTs provided sufficient 12-month data to be included in the meta-analysis [315-317]. With the 180-W (XPS) laser efficacy is comparable to TURP in terms of IPSS, Q_{max}, post voided residual volume, prostate volume reduction, PSA decrease and QoL questionnaires. The XPS laser prostatectomy is superior to TURP in terms of catheterisation time, lengths of hospital stay and time to stable health status.

The longest RCT using the 80-W KTP laser has a follow-up of only 12 months [315]. A case series showed durable functional outcomes with the 80-W KTP laser, with an overall re-treatment rate of 8.9% at 5 years [318]. Another case series of 500 patients treated with the 80-W system with a mean follow-up of 30.6 months reported a re-treatment rate of 14.8% [319]. At 12 months self-reported urinary incontinence was 2.9% with XPS and 3.0% with TURP. Surgical re-interventions were comparably low after 12 months.

Significant improvements in voiding parameters at a follow-up of 12 months were demonstrated urodynamically [320]. 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 [321]. The re-operation rate was higher after PVP (11% vs. 1.8%; p = 0.04) [321]. Similar improvement of IPSS, QoL, Q_{max}, or urodynamic parameters was reported from two RCTs with a maximum follow-up of 24 months [316, 322].

A multicentre case series of the 180-W laser demonstrated comparable safety and symptom improvement compared with the former Greenlight laser systems [323].

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 [314]. 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 [314]. According to the "Goliath-Study", 180-W Greenlight laser prostatectomy is non-inferior to TURP in terms of perioperative 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 12 months follow-up. There are more severe bleeding complications within 30 days after TURP and more mild bleeding complications after XPS laser prostatectomy over 12 months, leading to a comparable overall incidence between both techniques.

The Greenlight laser appears to be safe in high-risk patients under anticoagulation treatment [324-328]. In one study, anticoagul patients had significantly higher rates of bladder irrigation (17.2%) compared with those not taking anticoagulants (5.4%) [327]. Safety in patients with urinary retention, or prostates > 80 mL was shown in various prospective non-randomised trials [328-330].

The impact of Greenlight laser on sexual function and abnormal ejaculation was similar to that of TURP after 12 months [331]. In addition, no difference was reported between OP/TURP and Greenlight PVP for erectile function [332, 333]. IIEF-5 scores are maintained after treatment. However, in patients with preoperative IIEF-5 > 19, the postoperative IIEF-5 scores were significantly decreased at 6, 12, and 24 months [334].

Practical considerations: The 180-W XPS laser should be regarded as the reference for Greenlight laser prostatectomy in 2016. Many former studies were done with the out-dated former 80-W and 120-W. Results need to be interpreted accordingly. Long-term results from the Goliath Study (180-W XPS vs. TURP) are pending.

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 [335].

Efficacy: Case series, and two comparative studies of a 980 nm diode laser and the 120 W HPS laser, are available [336-342]. IPSS, QoL, Q_{max} , and PVR improved significantly in all studies compared to baseline and were similar compared to 120-W HPS laser, at 6 and 12 months [336, 337].

One RCT with a 12 month follow-up compared 980 nm diode laser with plasmakinetic enucleation and found equal clinical outcome, data supported by one RCT, comparing 980 nm diode laser vaporization vs. TUR-P within a 2-year follow-up [343], while redo TURP was more frequent in the diode laser group (online supplementary Table S.28). Adverse events and catheter time favoured the diode laser group [344]. One small RCT with a 6 months' follow-up comparing laser enucleation using a 1,318 nm diode laser with B-TURP reported similar efficacy and safety results (online supplementary Table S.28) [345]. Blood loss and hospitalisation time were in favour of laser enucleation.

Tolerability and safety: Published studies on 980 nm laser indicate high intraoperative safety, since no bleeding was reported, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% of patients [336, 337]. Post-operatively, a high rate of dysuria was reported [336, 337]. Fibre modifications led to a significant reduction [339]. In summary, high re-operation rates (8-33%) and persisting stress urinary incontinence (9.1%) were reported [336-338, 343].

Practical considerations: Diode lasers lead to immediate improvement of LUTS due to BPO and provide good haemostatic properties. Based on the limited number, mainly low quality RCTs and controversial data on the re-treatment rate, results on diode lasers 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 [335, 346]. Different applications, ranging from vaporisation (ThuVaP), vaporesection (ThuVaRP), and enucleation (ThuVEP/ThuLEP: similar enucleating techniques) are published.

Efficacy: A major drawback is the limited number of RCTs. One RCT with a 4-year follow-up compares ThuVARP to M-TURP, showing comparable efficacy and favourable re-operation rates in the ThuVaRP group [347] (online supplementary Table S.28). One RCT and one non-RCT compared ThuVaRP with M-TURP [348, 349], while two RCTs comparing ThuVaRP and B-TURP were published recently [350, 351]. 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 [352-355]. ThuLEP and HoLEP were compared in one RCT with 18-months of follow-up with comparable outcomes in both arms (online supplementary Table S.28) [356].

Tolerability and safety: Thulium laser prostatectomy shows high intra-operative safety in RCTs [347, 348], as

well as in case series in patients with large prostates [352], anticoagulation or bleeding disorders [353, 357]. Catheterisation time, hospital stay, and blood loss were shorter compared to TURP [348-350]. The rate of post-operative urethral strictures after ThuVaRP was 1.9%, the rate of bladder neck contracture was 1.8%, and re-operation rate was 0-7.1% during follow-up [348, 349, 358]. Urethral stricture after ThuVEP occurred in 1.6%, and the overall re-treatment rate was 3.4% (mean follow-up 16.5 months) [359]. No urethral and bladder neck strictures after ThuLEP were reported during the 18-month follow-up [356]. Recently a large series of complications after vapoenucleation reported adverse events in 31% of cases, with 6.6% complications > Clavien grade II [360]. 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% [357]. 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 postoperatively [361, 362].

Practical considerations: The limited number of RCTs and few studies with long-term follow-up (up to 48 months) supports the efficacy of thulium laser prostatectomy with the need for ongoing confirmation.

Recommendations	LE	GR
HoLEP and 532-nm laser vaporisation of the prostate are alternatives to 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 HoLEP are comparable with TURP or open prostatectomy.	1b	A
Thulium enucleation may be an alternative to TURP and HoLEP 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
ThuVaRP 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

HoLEP = holmium laser enucleation; LUTS = lower urinary tract symptoms; TURP = transurethral resection of the prostate; ThuVaRP = Tm:YAG vaporesection.

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 [363, 364].

A prostatic stent requires a functioning detrusor [365]. 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 [365].

Efficacy: Several small case studies on a range of stents of different designs and materials provide low level of evidence for their use. Online supplementary Table S. 29 describes the most important studies [363, 364, 366-369]. 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 blind-placement prostatic stent (BPS) for BPO [370].

The main representative of the permanent stents is the UroLume prosthesis. A systematic review identified 20 case series (990 patients), with differing follow-ups [371]. These studies reported relevant symptom improvement and Q_{max} increase [371]. 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 [371, 372].

The data on non-epithelialising prostatic stents was summarised in a systematic review on the efficacy of Memokath, a self-expanding metallic prostatic stent [373]. IPSS was reduced by 11-19 points and Q_{max} increased by 3-11 mL/s [373].

Tolerability and safety: In general, stents are subject to misplacement, migration, and poor tolerability because of exacerbation of LUTS and encrustation [365]. The main immediate 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 [365].

Recommendation	LE	GR
Offer prostatic stents as an alternative to catheterisation for 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.30 [374-379]. 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 [374]. The primary endpoint was meet at 3 months with a 50% reduction in AUA-SI from 22.1 to 11.0 points and remained stable up to 12 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 3 months and this result could still be confirmed at 12 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.

Recently, a multinational, RCT of 80 patients (conducted in nine European countries) evaluating PUL to TURP was published. At 12 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 3 to 6 months [380]. However, TURP resulted in much greater improvements in Q_{max} (+13.7 ± 10.4 mL/s) after 12 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 (change from -7.2 to -8.7 points), Q_{max} (3.8 to 4.0 mL/s), and QoL (-2.2 to -2.4 points) [379]. Sexual function was preserved with a small improvement estimated at 12 months.

A multicentre, prospective, non-randomised study on 64 patients evaluated effectiveness of PUL over 2 years [375]. At 2 weeks, IPSS improved by 42% and was maintained for 24 months. A similar therapeutic effect was also observed for Q_{max} which increased significantly by 45% from 8.3 to 12.0 mL/s after 2 weeks. This benefit was stable up to 2 years. However, at the 2-year follow-up, 20% of patients required additional treatment due to initial PUL failure [375].

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.

PUL 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 [374-378].

Practical considerations: An obstructed/protruding median lobe cannot be effectively treated, and the effectiveness in large prostate glands has not been shown yet. High quality studies are needed to compare the efficacy, safety and durability between PUL and other established invasive treatments.

Recommendation	LE	GR
Prostatic urethral lift (Urolift®) leads to objective and subjective short- and mid-term improvements. RCTs with longer follow-up are required.	1a	B

RCT = randomised controlled trial.

5.3.8 *Investigational operations*

5.3.8.1 *Intra-prostatic botulinum toxin injections (see supplemental online material)*

5.3.8.2 *Minimal invasive simple prostatectomy*

Mechanism of action: The term minimal invasive simple prostatectomy (MISP) includes the laparoscopic simple prostatectomy (LSP) and robot-assisted simple prostatectomy (RASP). The technique for LSP was first described in 2002 [381], while the first RASP was reported in 2008 [382]. Both LSP and RASP are performed using different personalised techniques, developed based on the transcapsular (Millin) or transvesical (Freyer) techniques of open simple prostatectomy (OSP). An extraperitoneal approach is mostly used for LSP, while a transperitoneal 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 intraoperative 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 OSP (WMD 37.8 min, p < 0.0001). There were no differences in improvements in Q_{max}, IPSS and perioperative complications between both procedures (see online supplementary Table S.32). Two recent retrospective series on RASP are now available which were not included in the meta-analysis which confirm these findings [383, 384]. 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 centers [383].

Tolerability and safety: In the largest series, the postoperative 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 an effective and safe treatment option, providing similar improvements in Q_{max} and IPSS as OP [385]. However, most studies are of retrospective nature. High quality studies are needed to compare the efficacy, safety, and hospitalisation between MISP and both OP and endoscopic methods. Long-term outcomes, learning curve and cost of MISP should also be evaluated.

Recommendation	LE	GR
MISP seems to be feasible in men with prostate sizes > 80 mL needing surgical treatment. Since more data are required, MISP remains under evaluation.	2	B

MISP = minimal invasive simple prostatectomy.

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. The online supplementary Table S.33 provides differential information about speed of onset and influence on basic parameters with 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.
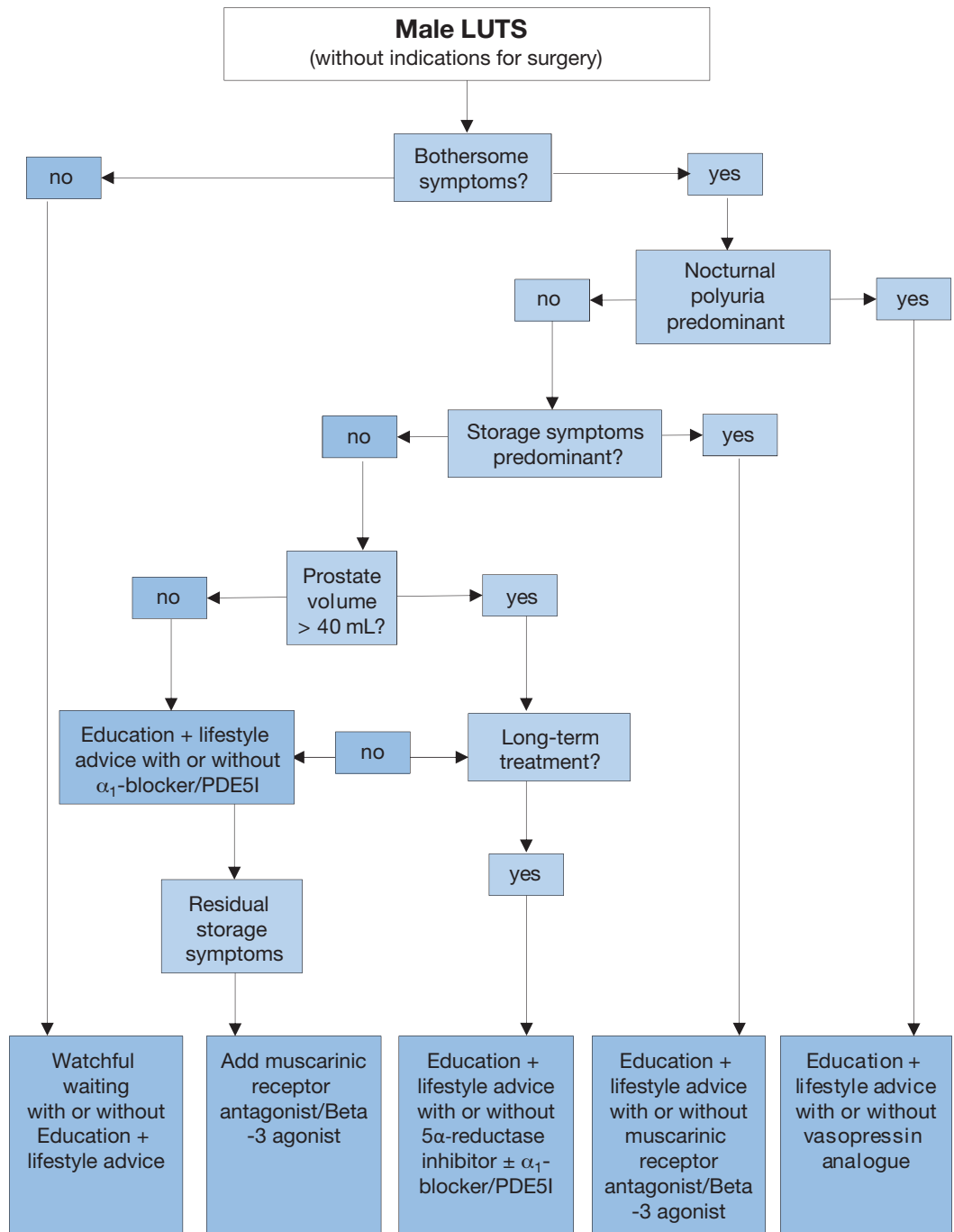
LUTS = lower urinary tract symptoms; PDE5I = phosphodiesterase type 5 inhibitors.

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.
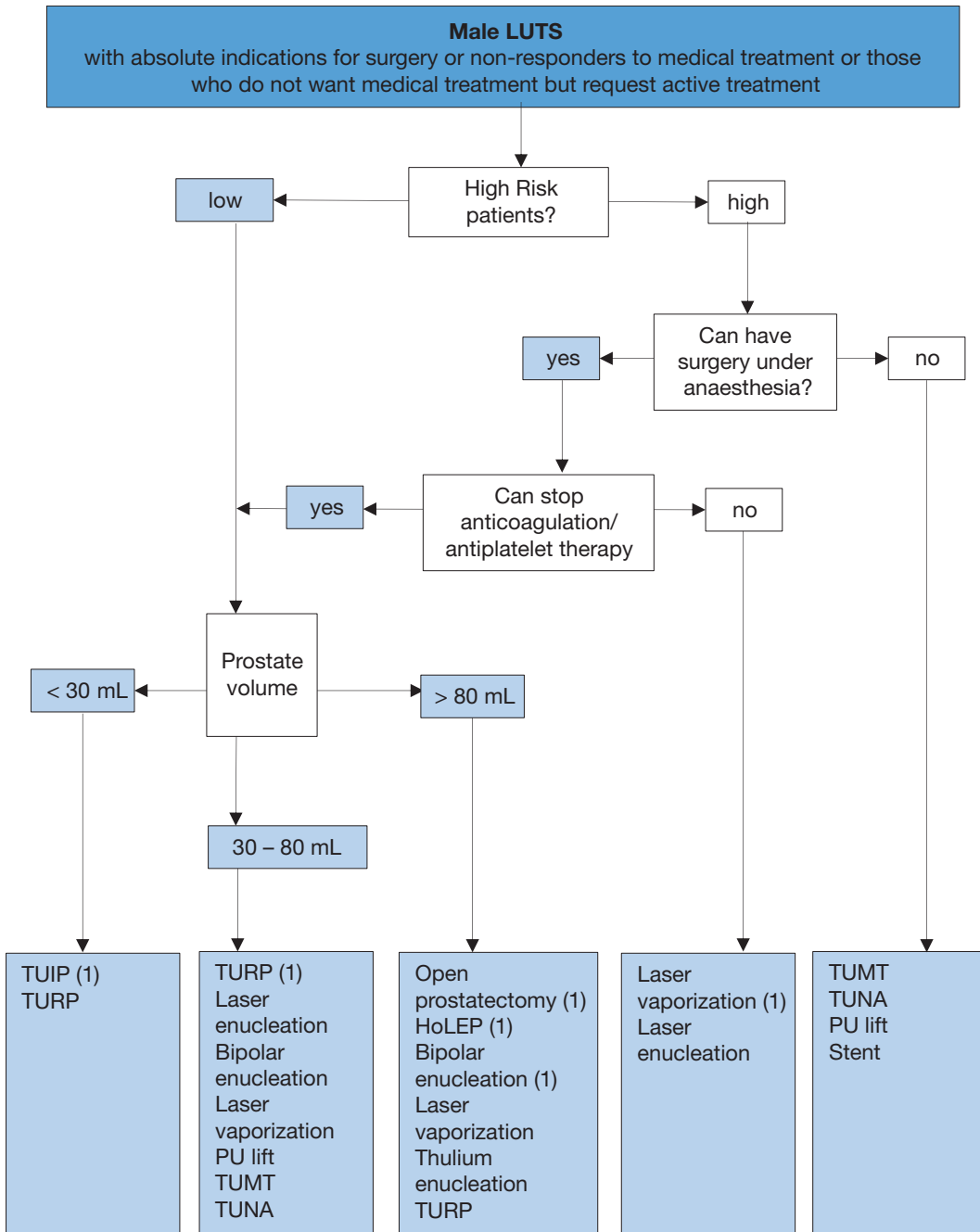
(1) Current standard/first choice. The alternative treatments are presented in alphabetical order.
Notice: Readers are strongly recommended to read the full text that highlights the current position of each treatment in detail.

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

This first iteration of an EAU Guideline for Nocturia in Male LUTS reports a systematic review of therapy, and emphasises the need to consider the wide range of possible causes. This summary print version is supplemented by a detailed online version (http://uroweb.org/guideline/ treatment-of-non-neurogenic-male-luts/).

Nocturia is defined as the complaint of waking at night to void [4]. 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)
Behavioural	Inappropriate fluid intake	"Bladder awareness" due to secondary sleep disturbance
Systemic	Water, salt and metabolite output	
Sleep disorder	Variable water and salt output	"Bladder awareness" due to primary sleep disturbance
LUTD		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 bother 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.
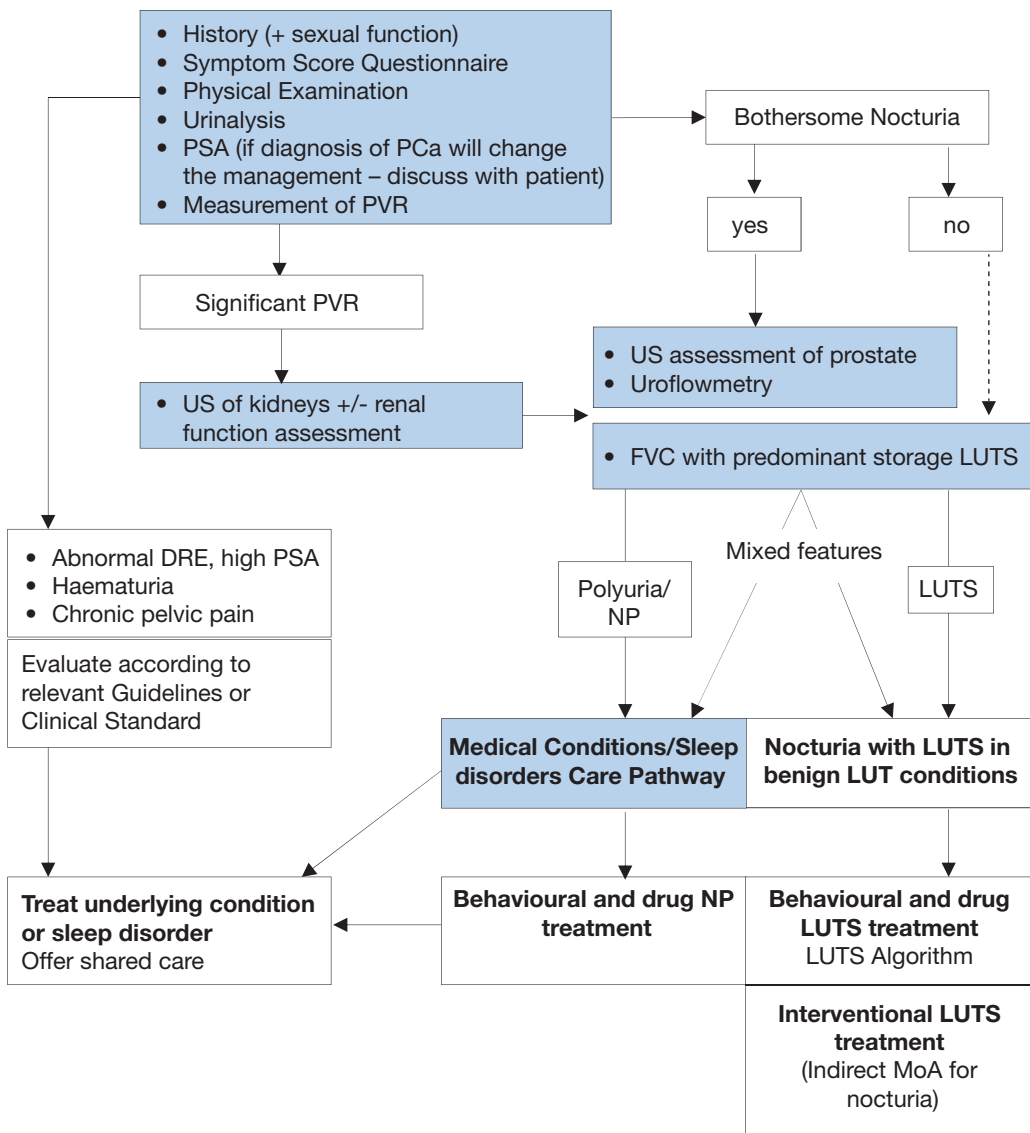
Assessment must establish whether the patient has polyuria, LUTS, sleep disorder or a combination. Therapy may be driven by the bother it causes, but non-bothersome nocturia may warrant assessment of a frequency volume chart (FVC), (indicated by the dotted line), depending on history and clinical examination since potential presence of a serious underlying medical condition must be considered.

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 [386]:

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 people aged over 65 [4]);
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 • Urological/LUTS evaluation • Nocturia symptom scores • Bladder diary		**Diagnosis of conditions causing NP** • Evaluate patient's known conditions • Screening for sleep disorders • Screening for potential causes of polyuria*
Conservative management Behavioural therapy • Fluid/sleep habits advice • Drugs for storage LUTS • (Drugs for voiding LUTS) • ISC/catherisation	**Conservative management** • Antidiuretic • Diuretics • Drugs to aid sleep	**Management** • Initiation of therapy for new diagnosis • Optimised therapy of known conditions * Potential causes of polyuria NEPHROLOGICAL DISEASE • Tubular dysfunction • Global renal dysfunction CARDIOVASCULAR DISEASE • Cardiac disease • Vascular disease ENDOCRINE DISEASE • Diabetes insipidus/mellitus • Hormones affecting diuresis/natriuresis NEUROLOGICAL DISEASE • Pituitary and renal innervation • Autonomic dysfunction RESPIRATORY DISEASE • Obstructive sleep apnoea BIOCHEMICAL • Altered blood oncotic pressure
Interventional therapy • Therapy of refractory storage LUTS • Therapy of refractory voiding LUTS		

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. AVP increases water re-absorption and urinary osmolality, so decreasing water excretion and total urine volume. AVP 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 [387], 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 17 cases of hyponatraemia and seven of hypertension. Headache was reported in 53 and nausea in 15.

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 α1-adrenergic antagonists [388], antimuscarinics [389-391], 5α-reductase inhibitors [392] and PDE5Is [393].

5.5.3.3   Other medications
Diuretics, agents to promote sleep [394], diuretics [395], non-steroidal anti-inflammatory agents (NSAIDs) [396] and phytotherapy [397]. 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
α1-adrenergic antagonists may be offered to men with nocturia associated with LUTS.	1b	B
Anti-muscarinic drugs may be offered to men with nocturia associated with overactive bladder.	1b	B
5α-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 PDE5Is 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.
LUTS = lower urinary tract symptoms; PDE5Is = Phospodiesterase 5 inhibitors.

6.   FOLLOW-UP

6.1   Watchful waiting (behavioural)
Patients who elect to pursue a WW policy should be reviewed at 6 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 α1-blockers, muscarinic receptor antagonists, PDE5Is or the combination of α1-blockers + 5-ARIs or muscarinic receptor antagonists should be reviewed 4-6 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 6 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 12 weeks and 6 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 > 10 years and if a diagnosis of PCa could alter management. A new baseline PSA should be determined at 6 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 3

and 7 as well as after 1 month, and if serum sodium concentration has remained normal, every 3 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 4-6 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 4 to 6 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

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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

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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 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.

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 with updates in 2012, 2013, 2014 and 2015. For this 2016 print updates were made to:
*   4.1 Conservative Management;
*   4.2.8 Oestrogen;
*   4.3.6.1 Bladder wall injection of botulinum toxin A.

2. METHODS

2.1 Introduction

For the 2016 Urinary Incontinence Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

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 [6]. 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. We are of the opinion 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.

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 and 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 methodology for questionnaire development was reviewed in the 5th International Consultation on Incontinence in 2012 [7].

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 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 have taken place in adults without 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 [8, 9]. In men ICIQ-UI-SF score does not differentiate UI types [10]. Some are responsive to change and may be used to measure outcomes, though evidence on their sensitivity is inconsistent [11-13].

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
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 2016 Abbreviations List in Appendix A.
** 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 [14].

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 UI.	3
Validated symptom scores measure the severity of UI.	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.	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 Questions
- 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 [15, 16]. 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 [17, 18]. 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 [19, 20]. Another study found that keeping a voiding diary had a therapeutic benefit [21].

A number of observational studies have demonstrated a close correlation between data obtained from voiding diaries and standard symptom evaluation [22-25].

Summary of evidence	LE
Voiding diaries of 3-7 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 3 and 7 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 Guideline for diagnosis and treatment of UTI [26].

3.4.1 Questions
- 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 [27] and should be included, with urine culture when necessary, in the evaluation of all patients with UI. Urinary incontinence may occur during symptomatic UTI [28] and existing UI may worsen during UTI [29]. The rate and severity of UI was unchanged after eradication of asymptomatic bacteriuria in nursing home residents [30].

Summary of evidence	LE
Urinalysis negative for nitrite and leucocyte esterase reliably excludes UTI.	1
UI may be a symptom during UTI.	3
The presence of a symptomatic UTI worsens symptoms of UI.	3
Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	GR
Preform 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-voiding residual volume

Post-voiding 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-voiding 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 [31-36] have led to the consensus that US measurement of PVR is preferable to catheterisation.

In peri- and postmenopausal women without significant LUTS or pelvic organ symptoms, 95% of women had a PVR < 100 mL [37]. In women with UUI, a PVR > 100 mL was found in 10% of cases [38]. Other research has found that a high PVR is associated with POP, voiding symptoms and an absence of SUI [37, 39-41].

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 [38].

Summary of evidence	LE
Lower urinary tract symptoms coexisting with UI are associated with a higher rate of PVR compared to asymptomatic subjects.	2

Recommendations	GR
When measuring post void residual urine volume, use ultrasound.	A
Measure post-voiding residual in patients with urinary incontinence who have voiding symptoms.	B
Measure post-voiding residual when assessing patients with complicated urinary incontinence.	C
Post-voiding 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. Numerous small studies of

multichannel cystometry have been done over many years in differing populations. Whilst in healthy women the same session repeatability has been shown to be poor [42], in those with incontinence it may be acceptable [43]. Measurement of urethral closure pressure (MUCP) correlates poorly with incontinence severity [44] and there is conflicting evidence about its reproducibility [45, 46]. One method of recording MUCP cannot be compared meaningfully to another [47].

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 [48]. 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 [49, 50], and normal healthy people may have urodynamic abnormalities.

The diagnostic accuracy of urethral pressure profilometry [44] and 'Urethral Retro resistance' is generally poor [51]. Urethral reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [52].

Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry, but the clinical relevance of this is uncertain [53, 54].

3.6.2.3   Does urodynamics influence the outcome of conservative therapy?
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 [55]. Subanalysis of an RCT comparing fesoterodine to placebo [56, 57] showed no predictive value for treatment response, by the urodynamic diagnosis of DO.

3.6.2.4   Does urodynamics influence the outcome of surgery for urinary incontinence?
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 [58] there was no difference in levels of UI or any secondary outcome at 12 months follow-up after surgery [59]. Another similar study was closed with only 59 women [60] after finding no difference in outcome. It was then redesigned so that patients in whom urodymanics 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 [61].

In observational studies there is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery [23, 25, 26, 62]. 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 [57].

The Panel recognise that it may be valuable to use urodynamic test results to choose the optimum surgical procedure but at the time of this review there is inconsistent evidence to show any predictive value that would support this approach.

3.6.2.5   Does urodynamics help to predict complications of surgery for UI?
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 preoperative PVR [66, 67].

3.6.2.6 Does urodynamics influence the outcome of treatment for post-prostatectomy urinary incontinence in men?

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 UI.	3
There is limited evidence that ambulatory urodynamics is more sensitive than conventional urodynamics for diagnosing SUI or DO.	2
There may be inconsistency between history and urodynamic results.	3
Preliminary urodynamics can influence the choice of treatment for UI, but does not affect the outcome of conservative therapy or drug therapy for SUI.	1a
Preoperative urodynamics in women with uncomplicated, clinically demonstrable SUI does not improve the outcome of surgery for SUI.	1b
There is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that pre-operative DO is associated with surgical failure of mid-urethral sling in women.	3
The presence of preoperative DO may be associated with persistence of urgency postoperatively	3
There is no evidence that urodynamics predicts the outcomes of treatment for post-prostatectomy incontinence in men.	4

Recommendations *(NB: Concerning only neurologically intact adults with urinary incontinence)*	GR
Clinicians carrying out urodynamics in patients with urinary incontinence should: • 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 Question
• 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 1-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 UI accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
24 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.

US 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 midurethral 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 overactivity, 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 UI.	2b
There is no consistent evidence that bladder (detrusor) wall thickness measurement is useful in the management of UI.	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 often 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 the prevalence of UI in women with type 2 diabetes is higher. 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 UI.	3

Recommendation	GR
Patients with UI 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 [49]. 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?

4.1.1.4 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 UI and pelvic organ prolapse.	3
There is no consistent evidence in adults, that treatment of constipation alone improves UI.	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

4.1.1.4.1   Research priority
Does the normalisation of bowel habit improve UI in patients who are constipated?

4.1.1.5   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 to choose 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

4.1.1.5.1   Question
For adults with UI, is one type of containment device better than another?

4.1.1.5.2   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 (2 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].

4.1.1.5.3   Question
For men or women with UI is one type of pad better than another?

4.1.1.5.4   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.

4.1.1.5.5   Question
For men or women with UI is one type of catheter or external collection device better than another?

4.1.1.5.6   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].

4.1.1.5.7 Question
For men and women with UI, are external pressure devices more effective than standard treatment and is one device better than another?

4.1.1.5.8 Evidence
A crossover RCT in 12 men with post-prostatectomy incontinence found a hinge-type penile clamp to be more effective than circular clamps for control of UI and 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 UI between intravaginal and intra-urethral devices [111]. There was no difference in outcome at 12 months in women with SUI between vaginal pessary alone; PFMT alone; and vaginal pessary + PFMT, although vaginal pessary was inferior to PFMT at three months for bother 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 SUI in men.	2a
Vaginal devices may improve SUI 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, and 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.

4.1.1.5.9 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 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 2 years [117].

Summary of evidence	LE
Reduction of caffeine intake does not improve UI.	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 UI during intense physical activity but not during common activities.	3
Strenuous physical activity does not predispose to UI for women later in life.	3
Moderate exercise is associated with lower rates of UI 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. Form 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. A recent 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 UI.	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 2 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 UI in women.	1b
Non-surgical weight loss in overweight and obese women improves UI.	1a
Surgical weight loss improves UI in obese women.	1b
Weight loss in obese women improves UI.	1b
Weight loss in obese adults with diabetes mellitus reduces the risk of developing UI.	1b

4.1.2.5   Smoking
Smoking cessation is now a generalised public health measure and has been shown to be associated with 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 Cochrane review [152].

Summary of evidence	LE
There is no evidence that smoking cessation will improve the symptoms of UI.	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 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 (9 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 re-training): A program 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 [49, 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 7 RCTs in which BT was compared to drug therapy alone and showed only a benefit for oxybutynin in cure and improvement of UI (RAI 2012).

BT 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 UI 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 UUI remains uncertain.	2
The combination of bladder training with antimuscarinic drugs does not result in greater improvement of UI 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]. PFMT 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 direct comparisons of treatments and 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 14 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 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 15-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, supported 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 2015 concluded that there was no overall benefit at 12 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 3 and 12 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 12 months [173].

Summary of evidence	LE
PFMT for Women with UI	
PFMT is better than no treatment for improving UI and QoL in women with SUI and MUI.	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 15-year follow-up.	2
PFMT commencing in the early postpartum period improves UI in women for up to 12 months.	1
PFMT for post-prostatectomy UI	
PFMT appears to speed the recovery of continence following radical prostatectomy.	1b
PFMT does not cure UI 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 health technology appraisals [152, 157] and three systematic reviews [49, 174, 175].

The reviews include analysis of 15 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 sub-analyses 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 (6 RCTs) concluded that, in the short-term, there was some evidence that electrical stimulation enhanced the effect of PFMT in the short term but not after six months. ES was also more effective than sham stimulation at six, but not 12 months. There were, however, more adverse effects (pain or discomfort) with electrical stimulation. [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 UI, ES may improve UI compared to sham treatment and antimuscarinics.	2
ES may add benefit to PFMT 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 12 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 12-week RCTs of PTNS against sham treatment [180, 181] one comparing PTNS to tolterodine, and a 3-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 anti-muscarinic 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 make 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
P-PTNS appears effective for improvement of UUI 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 3 years.	1b
P-PTNS has comparable effectiveness to tolterodine for improvement of UUI in women.	1b
No serious adverse events have been reported for P-PTNS in UUI.	3
There is limited evidence for effectiveness of T-PTNS.	2a
There is no evidence that P-PTNS cures UI.	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 PFMT, lasting at least 3 months, as a first-line therapy to women with stress urinary incontinence or mixed urinary incontinence.	A
PFMT programmes should be as intensive as possible.	A
Offer PFMT to elderly women with urinary incontinence.	B
Offer PFMT to post-natal women with urinary incontinence.	A
Consider using biofeedback as an adjunct in women with stress urinary incontinence.	A
Offer PFMT to men undergoing radical prostatectomy to speed recovery of incontinence.	B
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, P-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

PFMT = pelvic floor muscle training; P-PTNS = percutaneous posterior tibial nerve stimulation;
T-PTNS = transcutaneous posterior tibial nerve stimulation.

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) [183] 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 5 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 MUI than for SUI alone.	2
Electrical stimulation is equally effective for MUI and SUI.	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
Five systematic reviews of individual antimuscarinic drugs vs. placebo were reviewed for this section [157, 187-190] as well as studies published since these reviews up until September 2013. 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.

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 the most recent 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 of curing UI (95% CI)	Number needed to treat to achieve one cure of UI (95% CI)
Cure of incontinence				
Fesoterodine	2	2465	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	6304	1.5 (1.4-1.6)	9 (6-17)
Tolterodine (includes IR)	4	3404	1.2 (1.1-1.4)	12 (8-25)
Trospium (includes IR)	4	2677	1.7 (1.5-2.0)	9 (7-12)
Discontinuation due to adverse events				
			Relative risk of discontinuation (95% CI)	NNT of one discontinuation (95% CI)
Darifenacin	7	3138	1.2 (0.8-1.8)	
Fesoterodine	4	4433	2.0 (1.3-3.1)	33 (18-102)
Oxybutynin (includes IR)	5	1483	1.7 (1.1-2.5)	16 (8-86)
Propiverine (includes IR)	2	1401	2.6 (1.4-5)	29 (16-27)
Solifenacin	7	9080	1.3 (1.1-1.7)	78 (39-823)
Tolterodine (includes IR)	10	4466	1.0 (0.6-1.7)	
Trospium (includes IR)	6	3936	1.5 (1.1-1.9)	56 (30-228)

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].

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 incontinence 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].

Summary of evidence	LE
All formulations of fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, darifenacin and trospium, provide a significantly better rate of cure or improvement of UUI compared to placebo.	1a
All formulations of fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, darifenacin and trospium, result in higher rates of side effects compared to placebo.	1b

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 five systematic reviews [157, 176, 187, 189, 191]. 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 (12 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 in 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 3).

Table 3: Comparison of antimuscarinic drugs as reviewed in the 2012 AHRQ review [157]

Experimental drug vs. standard drug	No. of studies	Patients	Relative risk of curing UI (95% CI)
Efficacy			
Fesoterodine vs. tolterodine ER (continence)	2	3312	1.1 (1.04-1.16)
Oxybutynin ER vs. tolterodine ER (improvement)	3	947	1.11 (0.94-1.31)
Solifenacin vs. tolterodine ER	1	1177	1.2 (1.08-1.34)
Trospium vs. oxybutynin	1	357	1.1 (1.04-1.16)
Discontinuation due to adverse events			
			Relative risk of discontinuation (95% CI)
Solifenacin vs. tolterodine ER	3	2755	1.28 (0.86-1.91)
Trospium vs. oxybutynin	2	2015	0.75 (0.52 -1.1)
Fesoterodine vs. tolterodine	4	4440	1.54 (1.21-1.97)

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, 191]. 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, 191]. 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 [192, 193]. 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 no consistent evidence that one antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of UUI.	1a
The ER formulation of oxybutynin is superior to the ER and IR formulations of tolterodine for improvement of UUI.	1b
Solifenacin is more effective than tolterodine IR for improvement of UUI.	1b
Fesoterodine, 8 mg daily, is more effective than tolterodine ER, 4 mg daily, for cure and improvement of UUI, but with a higher risk of side effects.	1b
ER formulations and once-daily antimuscarinic drugs are generally associated with lower rates of dry mouth than IR preparations, although trial discontinuation rates are similar.	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
Oxybutynin IR or ER shows higher rates of dry mouth than the equivalent formulation of tolterodine.	1a
There is no evidence that any particular antimuscarinic agent is superior to another for improvement in QoL.	1a

4.2.3 Antimuscarinic drugs vs. non-drug treatment
The choice of drug vs. non-drug 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 an alternative non-drug treatment?

4.2.3.2 Evidence
More than 100 RCTs and high-quality reviews are available [158, 176, 189, 190, 194, 195]. 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. One RCT showed a substantial benefit for sacral neuromodulation compared with medical therapy [196]. In men with storage LUTS no difference in efficacy was found between oxybutynin and behavioural therapy [197]. The combination of BT and solifenacin in women with OAB conferred no additional benefit in terms of continence [198].

Two small RCTs [199, 200], reported a similar improvement in subjective parameters with either transcutaneous electrical nerve stimulation or T-PTNS. However, only oxybutynin treated patients showed significant improvements in objective urodynamic parameters (bladder capacity). The oxybutynin-treated group had more side effects. One study compared tolterodine ER to transvaginal/anal electrical stimulation without differences in UI outcomes [201]. One small RCT found that the addition of P-PTNS to tolterodine ER improved UI and QoL [202].

Summary of evidence	LE
There is no consistent evidence to show superiority of drug therapy over behavioural therapy for treatment of UUI.	1b
Behavioural treatment has higher patient satisfaction than drug treatment.	1b
There is no consistent evidence to show superiority of drug therapy over PFMT for treatment of UUI.	1b

4.2.3.3   Recommendations for antimuscarinic drugs

Recommendations	GR
Offer IR or ER formulations of antimuscarinic drugs for adults with urgency urinary incontinence.	A
If IR formulations of antimuscarinic drugs are unsuccessful for adults with urgency urinary incontinence, offer ER formulations or longer-acting antimuscarinic agents.	A
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 (< 30 days).	A

IR = immediate release; ER = extended release.

4.2.4   Antimuscarinic agents: adherence and persistence

Most studies on antimuscarinic medication are short term (12 weeks). Adherence in clinical trials is considered to be much higher than in practice.

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 [203]. Two recent open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at 2 years of 49-84% [204, 205]. The main drugs studied were oxybutynin and tolterodine IR and ER. Non-persistence rates were high for tolterodine at 12 months, and particularly high (68-95%) for oxybutynin.

Five articles reported 'median days to discontinuation' as between < 30 days and 50 days [206-210]. In a military health system where free medication was provided the median time to discontinuation extended to 273 days [207].

Data on adherence/persistence from open-label extension populations are questionable as these patients are self-selected to be compliant. Data from pharmacy databases is included in this section.

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 [207].

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 minorities more likely to discontinue or switch treatment).

In addition, the source of data influenced the adherence figures.

Summary of evidence	LE
Most patients will stop antimuscarinic agents within the first 3 months because of lack of efficacy, adverse events and/or cost.	2

4.2.5   ***Antimuscarinic agents, the elderly and cognition***
Limited trials have been conducted in elderly people with UI. Issues 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 are available [211, 212]. A community-based cohort study found a high incidence of cognitive dysfunction [213]. 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 [214].

Very few trials specifically investigated the cognitive changes associated with antimuscarinic agents. In general, these trials have measured CNS side effects in a non-specific way therefore, the impact of antimuscarinic agents on specific patient cohorts is poorly understood [215, 216]. There are studies on antimuscarinic effects in elderly persons [217], and in people with dementia with UUI [218].

4.2.5.2.1   Oxybutynin
There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults [215, 217, 219-223]. Recent evidence has emerged from a prospective cohort study showing cumulative cognitive deterioration associated with prolonged use of antimuscarinic medication including oxybutynin [224].

More rapid functional deterioration might result from the combined use of cholinesterase inhibitors with antimuscarinic agents in elderly patients with cognitive dysfunction [225].

4.2.5.2.2   Solifenacin
One pooled analysis [226] 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 [223]. 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 [227]. In patients with mild cognitive impairment, over 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most side effects compared to oxybutynin IR [222, 228].

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 [215]. Two RCTs in the elderly found a similar efficacy and side-effect profile to younger patients [229-232]. 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 [233].

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 [234, 235]. 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 [217].

4.2.5.2.5   Trospium chloride
Trospium is not supposed to cross the blood-brain barrier in healthy individuals. Two (EEG) studies in healthy volunteers showed no effect from trospium whilst tolterodine caused occasional changes and oxybutynin caused consistent changes [236, 237]. No evidence as to the comparative efficacy and side effect profiles of trospium in different age groups in available. However, there is some evidence that trospium does not impair cognitive function [218, 238] and that it is effective compared to placebo in the elderly [239].

4.2.5.2.6 Fesoterodine
There is no evidence comparing the efficacy and side effects of fesoterodine in elderly and younger patients. 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 [240]. Adherence was lower in the over-75 year-old group but the effect on mental status was not reported [204, 241, 242]. No difference between fesoterodine and placebo on cognitive function was reported in healthy older patients [243].

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.

4.2.5.2.8 Mirabegron
No trials of mirabegron have yet been reported in the elderly population with UI.

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 [213].

When starting anticholinergics in elderly patients, mental function should be assessed objectively and monitored [244]. No consensus exists as to the best mental function test to detect changes in cognition [225, 240].

4.2.5.2.10 Anticholinergic load
A number of medications have anticholinergic effects and their cumulative effects on cognition should be considered [245].

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, ACB) on cognitive function?

4.2.5.2.12 Evidence
There were no studies 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 [245, 246].

Two systematic reviews of largely retrospective cohort studies, showed a consistent association between long-term anticholinergic use and cognitive dysfunction [247, 248].

Longitudinal studies in older people over two to four years have found increased rate of decline in cognitive function for patients on definite and possible anticholinergics [249, 250].

Summary of evidence	LE
All antimuscarinic drugs are effective in elderly patients.	1b
In older people, the cognitive impact of drugs which have anticholinergic effects is cumulative and increases with length of exposure.	3
Oxybutynin may worsen cognitive function in elderly patients.	2
Solifenacin, darifenacin and fesoterodine have been shown not to cause increased cognitive dysfunction in elderly people.	1b
There is no evidence as to whether tolterodine and trospium chloride affect cognitive function.	3

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 non-pharmacological treatments first.	C
Use antimuscarinic drugs with caution in elderly patients who are at risk of, or have, cognitive dysfunction.	B
Do not use oxybutynin in elderly patients who are at risk of cognitive dysfunction.	A*
In older people who are being prescribed antimuscarinic drugs for control of urinary incontinence, consider modifications to other medications to help reduce anticholinergic load.	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 beta 3 agonist, available from 2013. 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.

Mirabegron has undergone evaluation in industry-sponsored phase 2 and phase 3 trials. Two systematic reviews of all currently reported studies assessing the clinical effectiveness of mirabegron [251, 252] 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 hrs than placebo, with no difference in the rate of common adverse events [251]. 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 hrs was found in people who had previously tried and those who had not previously tried antimuscarinic agents.

The most common treatment adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%) [251].

In a 12-month, active-controlled RCT of mirabegron 50/100 mg vs. tolterdine ER 4 mg, the improvement in efficacy seen at 12 weeks was sustained at 12-month evaluation in all groups. The reported dry rates at 12 months were 43%, 45% and 45% for mirabegron 50 mg, 100 mg and tolterodine 4 mg respectively [253].

No risk of QTc prolongation on electrocardiogram [254] and raised intraocular pressure [255] 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 [253].

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 [256].

Equivalent adherence was observed for tolterodine and mirabegron at 12 months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [253]. In mirabegron treated patients, improvement in objective outcome measures correlates directly with clinically relevant PROMs (OAB-q and PPBC) [257, 258].

Summary of evidence	LE
Mirabegron is better than placebo for improvement of UUI symptoms.	1a
There is no evidence that mirabegron is better than placebo for curing incontinence.	1b
Mirabegron is no more effective than tolterodine.	1b
Adrenergic-mediated side effects of mirabegron appear mild and not clinically significant in a trial setting.	1a
Discontinuation rates from mirabegron are similar to tolterodine in a trial setting.	1b

Recommendation	GR
Offer mirabegron to people with urgency urinary incontinence, but inform patients receiving mirabegron that the possible long-term side effects remain uncertain.	B

4.2.7 Drugs for stress urinary incontinence
Trials have focused on the effect of alpha-adrenoceptors in increasing the closure urethral pressure in women as a means of improving SUI.

A Cochrane review [259] found 22 trials of adrenergic drugs in women with predominant SUI in comparison to placebo or PFMT. Eleven of these trials involved phenylpropanolamine (withdrawn in some countries because of an increased risk of haemorrhagic stroke). The review found weak evidence that these drugs are better than placebo at improving UI in women. Comparative trials with PFMT gave inconsistent results. No new trials were published between 2007 and 2010. At present, these drugs are not licensed for use in UI.

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 two systematic reviews [190, 259] of 10 RCTs, and one subsequent RCT. The typical dose of duloxetine was 80 mg daily, with dose escalation up to 120 mg daily allowed in one study, over a period of 8-12 weeks. One RCT extended the observation period up to 36 weeks and used the Incontinence Quality of Life (I-QoL) score as a primary outcome.

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 IQoL as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [260], 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 1 year or more evaluated the long-term effect of duloxetine in controlling SUI, however both had high discontinuation rates [261, 262].

Duloxetine, 80 mg daily, which could be increased up to 120 mg daily, was investigated in a 12-week study in patients who had OAB but not SUI [263]. Episodes of UUI were also significantly reduced by duloxetine.

One study [264] compared PFMT + duloxetine vs. PFMT + placebo, for 16 weeks, followed by 8 weeks of PFMT alone in males with post-prostatectomy incontinence. Duloxetine + PFMT significantly improved UI, but the effect did not last to the end of the study, indicating that duloxetine only accelerates cure and does not increase the percentage of patients cured.

All studies had a high patient withdrawal rate of about 20-40% in short-term studies and up to 90% in long-term studies. Cause of the high withdrawal rate included 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.

Summary of evidence	LE
Duloxetine does not cure UI.	1a
Duloxetine, 80 mg daily improves SUI and MUI in women.	1a
Duloxetine causes significant gastrointestinal and CNS side effects leading to a high rate of treatment discontinuation.	1a
Duloxetine 80 mg daily, can improve SUI in men.	1b
Duloxetine 80 mg - 120 mg daily can improve UUI in women.	1b

Recommendations	GR
Duloxetine should not be offered to women or men who are seeking a cure for their incontinence.	A
Duloxetine can be offered to women or men who are seeking temporary improvement in incontinence symptoms.	B*
Duloxetine should be initiated using dose titration because of high adverse effect rates.	A

Downgraded based on expert opinion.

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 [265-267]. 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 recent Cochrane systematic review looked at the use of oestrogen therapy in postmenopausal women [265] given local oestrogen therapy. There is also a more recent narrative review of oestrogen therapy in urogenital diseases [268]. No new RCTs have been published up to September 2012. The Cochrane review (search date June 2012) found that vaginal oestrogen treatment improved symptoms of UI in the short term [265]. 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 2 years was seen in one trial [269].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. Current data do not allow differentiation among the various types of oestrogens or delivery methods. The ideal treatment duration and the long-term effects are uncertain. One RCT compared oestradiol ring pessary with treatment with oxybutynin ER showing no difference in outcomes [270].

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 [271-274]. In a single RCT use of raloxifene was not associated with development or worsening of UI [275]. Three small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [49, 276, 277].

Summary of evidence	LE
Vaginal oestrogen therapy improves UI for post-menopausal women in the short term.	1b
There is no consistent evidence that vaginal oestrogen therapy cures SUI.	2
There is no evidence that one method of vaginal delivery is better than another.	4
Neoadjuvant or adjuvant use of local oestrogens are ineffective as an adjunct to surgery for UI.	2
Systemic hormone replacement therapy using conjugate equine oestrogens in previously continent women increases the risk of developing UI and worsens pre-existing UI.	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 should be long-term and in an appropriate dose.	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 on nocturnal incontinence. Two RCTs have compared desmopressin to placebo with daytime UI as an outcome measure. Improved continence was shown during the first 4 hours after taking desmopressin in women [278]. The continuous use of desmopressin improved frequency and urgency, but did not improve UI in men and women with OAB [279]. 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).

Summary of evidence	LE
The risk of UI is reduced within 4 hours of taking oral desmopressin, but not after 4 hours.	1b
Continuous use of desmopressin does not improve or cure UI.	1b
Regular use of desmopressin may lead to hyponatraemia.	3

Recommendations	GR
Offer desmopressin to patients requiring occasional short-term relief from daytime urinary incontinence and inform them that this drug is not licensed for this indication.	B
Do not use desmopressin for long-term control of urinary incontinence.	A

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 [280]. In another study (n = 1380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [281]. Similar results were found for solifenacin [282, 283].

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 [284].

Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of respective subpopulations [285].

Summary of evidence	LE
Limited evidence suggests that antimuscarinic drugs are effective for improvement of the UUI component in patients with MUI.	2
Duloxetine is effective for improvement of both SUI and UUI in patients with MUI.	1b

Recommendations	GR
Treat the most bothersome symptom first in patients with mixed urinary incontinence.	C
Offer antimuscarinic drugs 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) [58] 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 LUTD is reviewed in the EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction [286].
• 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 in 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 think 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 1 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 12 months [287-297]. The overall patient-reported cure rate was 75%. There was weak evidence of higher clinician-reported cure rates at 12 months after mid-urethral sling (83%) compared to colposuspension (78%) [290-297]. However, longer term follow-up for up to 5 years reported no difference in effectiveness, though the numbers of participants lost to follow-up was high [76, 289]. 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) [288, 290, 298-300].

Transobturator route vs. retropubic route
The EAU Panel meta-analysis identified 34 RCTs (5786 women) comparing insertion of the mid-urethral sling by the retropubic and transobturator routes. There was no difference in cure rates at 12 months in either patient-reported or clinically reported cure rates (77% and 85%, respectively) [4]. 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 pain at 12 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 [301]. 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 [302].

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 definition. 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 use existing data to make 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 (eg 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 [303] 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 [4] were consistent with those of the Cochrane systematic review [301], 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 [304] and the difference may result from the Panel's decision to only consider trial data with at least 12 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 [305]. One recent RCT [306] and another cohort study [307] 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.

An 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 [308]. 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 1 year [309]. 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 [310].

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 [311].

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 [312].

Summary of evidence	LE
Compared to colposuspension, the retropubic insertion of a mid-urethral synthetic sling provides equivalent patient-reported cure of SUI at 5 years.	1a
Mid-urethral synthetic sling inserted by either the transobturator or retropubic route provides equivalent patient-reported outcome at 12 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 12 months than 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 SUI 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.	1c
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 UI.	1
The risk of failure from surgical repair of SUI, 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 SUI, coital incontinence is likely to improve.	3
Overall, sexual function is unlikely to deteriorate following SUI 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 gold standard 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 [286, 313-315], but no RCTs comparing any operation to a sham procedure were identified.

Open colposuspension
The Cochrane review [316] included 46 trials in which 4738 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 5 years and 21% over 5 years. The re-operation rate for UI was 2%. Colposuspension was associated with a higher rate of development, at 5 years, of enterocoele/ vault/cervical prolapse (42%) and rectocele (49%) compared to tension-free vaginal tape (TVT) (23% and 32%, respectively). The rate of cystocoele 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 5 years with colposuspension but otherwise reported similar outcomes.

Anterior colporrhaphy
Anterior colporrhaphy is now considered an obsolete operation for UI. In a Cochrane review [330], 10 trials compared anterior colporrhaphy (385 women) with colposuspension (627 women). The failure rate for UI at follow-up of up to 5 years was worse for anterior colporrhaphy with a higher requirement for re-operation for incontinence.

Autologous fascial sling
The Cochrane review [314, 317] described 26 RCTs, including 2284 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 [48] showing superiority of fascial sling, most of the studies were of variable quality, with a few very small studies, and a short follow-up. The meta-analysis showed that fascial sling and colposuspension had a similar cure rate at 1 year. Colposuspension had a lower risk of voiding difficulty and UTIs, but a higher risk of bladder perforation.

In 12 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 [310].

Laparoscopic colposuspension
The Cochrane review [313] identified 22 RCTs, of which 10 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-uretheral slings, the subjective cure rates were similar, while the objective cure rate favoured the mid-urethral sling at 18 months. Complication rates were similar for the two procedures and operating times were shorter for the mid-urethral sling. Comparisons of colposuspension to mid-uretheral sling are covered in section 4.3.1.1.

Summary of evidence	LE
Autologous fascial sling is more effective than colposuspension for improvement of SUI .	1b
Laparoscopic colposuspension has similar efficacy to open colposuspension for cure of SUI and a similar risk of voiding difficulty or de novo 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 UTI.	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 [318, 319] and one independent systematic review [320], which reported on 12 RCTs or quasi-RCTs of injectable agents. In general, the trials were only of moderate quality and small with many of them had being reported only in abstract form. Wide confidence intervals meant a meta-analysis was not possible. Since the Cochrane review, two further RCTs have been reported [321, 322].

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 [323]. 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 [49, 324].

Another trial found that a peri-urethral route of injection can carry a higher risk of urinary retention compared to a transurethral injection [325]. A recent small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [321].

Summary of evidence	LE
Peri-urethral injection of bulking agent may provide short-term improvement in symptoms (3 months), but not cure, in women with SUI.	2a
Repeat injections to achieve therapeutic effect are often required.	2a
Bulking agents are less effective than colposuspension or autologous sling for cure of SUI.	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 for surgery for uncomplicated stress urinary incontinence in women	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 Neurogenic Lower Urinary Tract Dysfunction [286]. 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 [326] up till 2008 and the subject has also been reviewed by Ashok [327] and Lovatsis *et al.* [328]. 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 [329]. 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 [300].

Post-hoc subgroup analysis of high-quality RCTs comparing one procedure to another have shown conflicting evidence of relative effectiveness [74, 310, 330, 331]. 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 [332].

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 [333, 334], whilst other research has shown inferior outcomes for secondary surgery [335, 336]. 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 [337]. 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 SUI.	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 SUI, 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 [16].

Artificial urinary sphincter (AUS)
A previous review of mechanical devices concluded that there was insufficient evidence to support the use of AUS in women [338].

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 1 month to 25 years [339-342]. 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 10 years) and explantation (5.9-15%). In a retrospective series of 215 women followed-up for a mean of 6 years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [342]. Peri-operative injury to the urethra, bladder or rectum was also a high-risk factor for explantation [340].

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 4 years but the device has undergone redesign and more up-to-date evidence is awaited [343]. Early reports of laparoscopically implanted AUS do not have sufficient patient populations and/or sufficient follow-up to be able to draw any conclusions [344, 345].

Adjustable compression device (ACT)
There are four case series (n = 349), with follow-up ranging from 5 to 84 months [346-349]. 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 SUI caused by sphincter insufficiency.	3
Implantation of the ACT device may improve complicated UI.	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 mutichannel 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 AUS or ACT that, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	C

AUS = artificial urinary sphincter; ACT = adjustable compression therapy.
* 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 [350]. After prolapse surgery 434 of 2125 women (20.4%) reported new subjective SUI, in 16 trials. New voiding dysfunction was reported in 109 of 1209 (9%) women, in 12 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 [351], the other compared vaginal repair with and without a mid-urethral sling [352]. In both trials addition of an anti-incontinence surgery reduced the risk of SUI at 12 months. In one trial there was a higher rate of adverse events reported in the combined surgery group [352]. This was also the finding of the Cochrane review and meta-analysis.

Two trials addressed post-operative SUI in patients who had had SUI preoperatively. Borstad *et al.*, in a multi-center trial randomised women with POP and SUI to have a tension-free vaginal tape (TVT) at the time of prolapse repair or 3 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 [353].

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 [354]. 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 mid-urethral slings generally have 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 < 12 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 postprolapse 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 [352].

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 3 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 [355]. Kummeling *et al.* assessed the effect of a modified laparosocopic sacrocolpopexy on urodynamic parameters and reported an improvement with no evidence to support a concomitant prophylactic colposuspension [356]. Lee *et al.* assessed the value of pre-op UDS and 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 [357].

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 [358]. 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 [359]. In a further study occult SUI was only detected by a pessary test in 19% of patients, not by urodynamics, history or clinical examination [360].

Summary of evidence	LE
Women with prolapse + UI	
Surgery for POP + SUI shows a higher rate of cure of UI in the short term than POP surgery alone	1a
There is conflicting evidence on the relative long term benefit of surgery for POP + SUI vs. POP surgery alone	1b
Combined surgery for POP+SUI carries a higher risk of adverse events.	1b
Continent women with POP	
Are at risk of developing UI post-operatively.	1a
The addition of a prophylactic anti-incontinence procedure reduces the risk of post-operative UI.	1b
The addition of a prophylactic anti-incontinence procedure increases the risk of adverse events.	1b
Women with POP and OAB	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of OAB.	3
Women with prolapse and occult SUI	
Surgery for POP + occult SUI shows a higher rate of cure of occult SUI in the short-term than POP surgery alone.	1a
Combined surgery for POP + SUI carries a higher risk of adverse events than POP surgery alone.	1b

Recommendations for women requiring surgery for bothersome POP 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 POP without symptomatic or unmasked stress urinary incontinence	
Warn women that there is a risk of developing de novo 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 laying 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.

1.   In a woman with the clinical suspicion of having an urethral diverticulum, what is the best test to confirm the diagnosis?

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 video cystourethrography VCUG [361]. 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 [362]. Dwarkasing *et al.* also reports 100% specificity and sensitivity of MRI in a case series of 60 patients [363]. However, in a case series of 41 patients, a study reported 25% discrepancy between MRI and surgical findings [364].

2.   In a woman who has a bothersome urethral diverticulum, what is the relative effectiveness of available surgical treatments?

4.3.4.1   Surgical treatment

No RCTs were found. Surgical removal is the most commonly reported treatment in contemporary cases series. However, recurrence may occur; Han *et al.* found a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticulum within 1 year [365], 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 [366]. SUI may occur in up to 20% of women after diverticulectomy, requiring additional correction [367-370]. 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 [371].

Summary of evidence	LE
MRI has good sensitivity and specificity for the diagnosis of urethral diverticula, however there is a risk of mis-diagnosis 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 de novo SUI.	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*

4.3.5.1   *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 [372, 373].

4.3.5.1.1 Question
In men with post-prostatectomy incontinence or SUI, does injection of a urethral bulking agent cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.1.2 Evidence
Most studies are case series with small sample sizes. Small cohort studies showed a lack of benefit using a number of different materials [374, 375]. However, polyacrylamide hydrogel resulted in limited improvement in QoL without curing the UI [374]. A Cochrane review on the surgical treatment of post-prostatectomy incontinence found only one study that fulfilled the inclusion criteria [376]. 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

4.3.5.2   Fixed male sling
As well as 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) [377].

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 [378].

4.3.5.2.1 Question
In men with post-prostatectomy SUI, does insertion of a fixed suburethral sling cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.2.2 Evidence
Concerning the surgical treatment of post-prostatectomy incontinence, three recent literature reviews are available [379-381]. There are a large number of uncontrolled case series concerning men implanted with several types of slings [382, 383].

For the repositioning sling (AdVance), the benefit after a mean follow-up of 3 years has been published on 136 patients [384]. Earlier data were available from other cohort studies, totalling at least 614 patients with a mean follow-up of between 3 months and 3 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 [382]. Post-operative voiding dysfunction occurred in 5.7-1.3%, while erosions and chronic pain were uncommon (0-0.4%) [378, 384-386]. 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

4.3.5.3   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.

4.3.5.3.1   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?

4.3.5.3.2   Evidence
There are no prospective 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.

Remeex® system
For the Remeex® system, only two abstracts, with conflicting findings, have been published. One study followed 19 patients for nearly 7 years and reported 70% success, with no explants, infections or erosions. The second study followed 14 patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% [387].

Argus® system
Data on the Argus® system has been reported for 404 men, but only four series have reported on more than 50 patients [388, 389], 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% [389]. Infection of the device occurred in 5.4- 8% [388]. Erosions were reported in 5-10% [390]. Urethral perforations occurred in 2.7-16% [388]. Pain at the implant site was usually only temporary, but chronic pain has been reported [388, 390]. These complications resulted in explantation rates of 10-15% [389].

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 [391, 392].

Summary of evidence	LE
There is limited evidence that adjustable male slings can cure or improve SUI 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

4.3.5.4   Compression devices in males
External compression devices can be divided into two types: circumferential and non-circumferential compression of the urethral lumen [379]. 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.

4.3.5.4.1   Question
In men with post-prostatectomy SUI, does insertion of an external compression device cure SUI, improve QoL, or cause adverse outcomes?

4.3.5.4.2   Evidence
Artificial urinary sphincter
Although the AUS is considered to be the standard treatment for men with SUI, there are two systematic reviews [376, 381] presenting limited evidence, of generally poor quality, except for one RCT comparing AUS

with bulking agents [372]. A continence rate of about 80% can be expected, while this may be lower in men who have undergone pelvic radiotherapy [379].

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 [393]. Another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [394].

The transcorporeal technique of placement can be used for repeat surgery but evidence of effectiveness is lacking [395]. 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 [396, 397]. Patients who experienced complete continence after AUS implantation had a higher erosion risk [398]. One small series reported results of AUS implantation after failure of previous Advance sling, showing no difference in efficacy between secondary and primary implantation [399].

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 [400]. 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) [401]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [381, 402-405]. A questionnaire study showed that 50% of patients were still bothered significantly by persistent incontinence [406]. 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 AUS implantation is effective for cure of SUI 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 SUI.	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 for surgery in men with stress urinary incontinence	GR
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 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

AUS = artificial urinary sphincter; ACT = artificial compression device.
* 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 [407, 408]. 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 (CIC) [409].

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) 1105 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 5 episodes of UUI, around 12 micturitions per day and small PVR. At week 12, 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 [410].

QoL was substantially improved in the onabotA arm, as shown by the more than 60% of positive responses in the TBS questionnaire at week 12, which was doubled 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 [411], 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 2 RCTs was 24 weeks [409, 410].

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 6 months [412]. However, patients receiving onabotA were more likely to have cure of UUI (27% vs. 13%, p = 0.003), but also had higher rates of urinary retention during the initial 2 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 [413].

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 UUI 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 PVR 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 UUI, 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 antimuscarinic therapy.	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 [414] 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 6 months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at 6 months compared to 1.6% of the control group [196]. The other RCT [415] achieved similar results, although these patients had already been included in the first report [196]. However, Weil *et al.* [431] 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 17 case series of patients with UUI, who were treated early in the experience with sacral nerve stimulation were reviewed [416]. 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 4 years [417, 418] reported continued success (> 50% improvement on original symptoms) by about 50 of patients available for follow-up. Cure rates for UUI were 15% [418].

Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33-41% [417, 418]. In a sub-analysis 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 [419].

Summary of evidence	LE
Sacral nerve neuromodulation is more effective than continuation of failed conservative treatment for cure of UUI, but no sham controls have been used.	1b
In those patients who have been implanted, at long-term 50% improvement of UUI 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 [420, 421].

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 [422]. 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%) seemed to be less satisfactory than for patients with neurogenic UUI (90%).

Adverse effects were common and have been summarised in a review over 5-17 years of more than 267 cases, 61 of whom had non-neurogenic UUI [423]. In addition, many patients may require clean intermittent self-catheterisation to obtain adequate bladder emptying (Table 4).

Table 4: 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 [424]. Two case series [425, 426] 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 [420].

Summary of evidence	LE
There is limited evidence on the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic DO.	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 UI.	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
Life-long follow-up is recommended for 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 [427].

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 [310]. 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) [428]. A comparison of two parallel cohorts of patients undergoing surgery for SUI, with and without DO, found inferior outcomes in women with MUI [429].

One cohort of 450 women, showed that in urgency-predominant MUI, the success rate fell to 52% compared to 80% in stress-predominant MUI [430]. In a study with 1113 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 [431].

Overall, the outcome for women with pre-existing urgency incontinence remains uncertain.

Summary of evidence	LE
Women with MUI are less likely to be cured of their UI by SUI surgery than women with SUI alone.	1c
The response of pre-existing urgency symptoms to SUI 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 UI; 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 [432]. 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 1 year [309]. 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 [310].

Another RCT compared immediate TVT vs. delayed TVT in older women, confirming significant efficacy for the operated women, but the cohort as a whole suffered higher complication rates, particularly bladder perforation (22%) and urinary retention (13%) [311].

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 [312].

Cohort studies have shown the effectiveness of onabotulinum toxin A injections in the elderly and frail elderly [411, 433], 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 SUI, 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.

```
┌─────────────────────────────────┐
│  Women presenting with urinary  │
│           incontinence          │
└─────────────────────────────────┘
                │
                ▼
┌──────────────────────────────────┐        ┌──────────────────────────────────────┐
│ Initial assessment               │───────▶│ • Haematuria                         │
│ • History                     A  │        │ • Pain                               │
│ • Physical examination        A* │        │ • Recurrent UTI                      │
│ • Questionnaire optional      B* │        │ • Grade 3 or symptomatic prolapse    │
│ • Voiding diary               A  │        │ • Previous pelvic radiotherapy       │
│ • Urinalysis                  A* │        │ • Previous surgery for UI            │
│ • Post void residual             │        │ • Pelvic mass                        │
│   if voiding difficulty       B  │        │ • Suspicion of fistula               │
│ • Pad test if quantification     │        └──────────────────────────────────────┘
│   of leakage is desired       C  │                        │
└──────────────────────────────────┘                        ▼
                │                              ┌──────────────────────┐
                │                              │       Further        │
                │                              │     assessment       │
                │                              └──────────────────────┘
                ▼
┌──────────────────────────────────┐
│        Discuss management        │
└──────────────────────────────────┘
```

Individualised behavioural and physical therapies including pelvic floor muscle training **A**

Stress incontinence	Mixed incontinence	Urgency incontinence

Advise on bowels, drugs, co-morbidity, fluid intake **C**
Advise on weight loss **A**
Offer pads or other containment device if needed **A***
Offer desmopressin for short-term symptom relief **B**
Offer timed or promoted voiding in elderly/care-dependent people **A**

Anti-muscarinics **A**
or mirabegron **B**

No response

Consider P-PTNS **B**

Failed conservative or drug therapy - discuss surgical options

```
                        ┌─────────────────────────┐
                        │   Surgical treatment    │
                        │       in women          │
                        └─────────────────────────┘
                                   │
         ┌─────────────────────────────────────────────────────────┐
         │          Failed conservative or drug therapy             │
         └─────────────────────────────────────────────────────────┘
              │                      │                      │
         ┌─────────────────────────────────────────────────────────┐
         │   Offer urodynamics if findings may change choice of     │
         │   surgery                                          B     │
         └─────────────────────────────────────────────────────────┘
              │                      │                      │
      ┌──────────────┐       ┌──────────────┐       ┌──────────────┐
      │    Stress    │       │    Mixed     │       │   Urgency    │
      │ incontinence │       │ incontinence │       │ incontinence │
      └──────────────┘       └──────────────┘       └──────────────┘
```

Stress predominant   Urgency predominant

```
      ┌──────────────┐                       ┌────────────────────────┐
      │  Offer MUS   │                       │ Advise onabotulinum-    │
      │      A       │                       │ toxin A                 │
      └──────────────┘                       │ or                      │
              │                              │ sacral nerve stimulation│
              │                              │          A              │
              │                              └────────────────────────┘
              │                                         │
      ┌──────────────────┐                   ┌────────────────────────┐
      │ Offer fascial    │                   │ Discuss bladder         │
      │ sling or         │                   │ augmentation or         │
      │ colposuspension  │                   │ urinary diversion       │
      │ if MUS           │                   │          C              │
      │ unavailable      │                   └────────────────────────┘
      │       A          │
      └──────────────────┘
              │
         ┌──────────┐
         │ Failure  │
         └──────────┘
              │
      ┌──────────────────┐
      │ Re-evaluate      │
      │ patient and      │
      │ consider         │
      │ second-line      │
      │ surgery          │
      │       A          │
      └──────────────────┘
```

*Based on expert opinion

Figure 2: Management and treatment of men presenting with urinary incontinence.

Men presenting with urinary incontinence

Initial assessment
- History   A*
- Physical examination   A*
- Questionnaire optional   B
- Voiding diary   A
- Urinalysis   A*
- Post void residual if voiding difficulty   B
- Pad test if quantification of leakage is desired   C

- Haematuria
- Pain
- Recurrent UTI
- Previous pelvic radiotherapy
- Abnormal DRE
- Findings suspicious of voiding dysfunction

Further assessment

Discuss management options

Individualised behavioural and physical therapies including pelvic floor muscle training

Stress incontinence

Mixed incontinence

Urgency incontinence

Advise on bowel function, drugs, co-morbidity, fluid intake   C
Advise on weight loss   A
Offer pads or other containment device if needed   A*
Offer desmopressin for short term symptom relief   B
Offer timed or promoted voiding in elderly/care-dependent people   A

Anti-muscarinics
A
or mirabegron
B

No response

Consider P-PTNS
B

Failed conservative or drug therapy - discuss surgical options

```
                    ┌─────────────────────────────┐
                    │      Surgical treatment      │
                    │         in men with UI       │
                    └─────────────────────────────┘

       ┌───────────────────────────────────────────────────────┐
       │            Failed conservative or drug therapy          │
       └───────────────────────────────────────────────────────┘

       ┌───────────────────────────────────────────────────────┐
       │  Perform urodynamics, cystoscopy and consider imaging   │
       │  of lower urinary tract                                 │
       │   • to exclude bladder outlet obstruction               │
       │   • if the result would alter the choice of surgery     │
       └───────────────────────────────────────────────────────┘
```

Stress incontinence	Mixed incontinence	Urgency incontinence

Stress predominant

Urgency predominant

```
┌───────────────────────────────┐
│  Offer AUS to men with PPI     │
│  depending on severity         │
│              B                 │
└───────────────────────────────┘

┌───────────────────────────────┐
│  Consider fixed sling for men  │
│  with PPI                      │
│              B                 │
└───────────────────────────────┘
```

```
┌───────────────────────────────┐
│  Advise onabotulinumtoxin A    │
│              or                │
│  sacral nerve stimulation      │
│             B**                │
└───────────────────────────────┘

┌───────────────────────────────┐
│  Discuss bladder augmentation  │
│  or urinary diversion          │
│              C                 │
└───────────────────────────────┘
```

* Based on expert opinion

** Available evidence on onabutulinumtoxinA and sacral nerve stimulation refers mainly to women.

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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://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
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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 on 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.

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 shorter reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Neuro-Urology Guidelines. These versions are abridged and therefore may require consultation with the full text version. An updated summary has also been published in European Urology [4]. All are available through the EAU website: http://www.uroweb.org/guideline/neuro-urology/.

1.4 Publication history

The EAU published the first Neuro-Urology Guidelines in 2003 with updates in 2008, 2014, and 2015. For this 2016 print updates were made to:

- Chapter 3.1: The summary table on epidemiology of neuro-urological disorders has been revised. (Table 1);
- Chapter 3.2: The Definitions useful in clinical practice table has been updated (Table 2), as well as Table 3 Definitions useful when interpreting urodynamic studies;
- Chapter 3.3: Diagnostic evaluation, new figures have been included, as well as a new table (Table 4) presenting an overview of available patient questionnaires;
- Chapter 3.4: Non-invasive conservative treatment – inclusion of the systematic review results (Tibial nerve stimulation for treating neuro-urological patients: a systematic review and meta-analysis [5]).

1.5 Background

The function of the LUT is mainly storage and voiding of urine, which is regulated by the nervous system that coordinates 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 dysfunctions, 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 [6], 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 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 [7]. 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 2016 Neuro-Urology Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.

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 2016 Neuro-Urology Guidelines update are:
1.   Tibial nerve stimulation for treating neurogenic lower urinary tract dysfunction: a systematic review and meta-analysis [5].
2.   Transcutaneous electrical nerve stimulation for treating neurogenic lower urinary tract dysfunction: a systematic review [8].
3.   Which measures are available to evaluate sexual function/dysfunction in adult neuro-urological patients and which are the most appropriate [9]?

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 [10]. 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 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   Future goals

The results of ongoing and new systematic reviews will be included in the 2017 update of the Neuro-Urology Guidelines. Ongoing systematic reviews include:

*   What is the long-term effectiveness and complication rate for bladder reconstructions/substitution and incontinent urinary diversions in neuro-urological patients?
*   In neuro-urological patients, is the long-term use of repetitive intra-detrusor injection of botulinum toxin A clinically and urodynamically effective?
*   What are the definitions of urinary tract infections in neurogenic bladder dysfunction?
*   What are the benefits and harms of continent catheterisable stomas/tubes to treat bladder emptying difficulties in neuro-urological adult patients?
*   What is the prognostic value of urodynamic findings in predicting upper urinary tract damage?
*   Alpha-blockers in the treatment of voiding dysfunction in neuro-urological patients.

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 systems 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 frequently small sample sizes, resulting in low level of evidence in most published data (summarised in Table 1).

Table 1: Epidemiology of Neuro-Urological Disorders

Suprapontine and pontine lesions and diseases		
Neurological Disease	**Frequency in General Population**	**Type and Frequency of Neuro-Urological Symptoms**
Cerebrovascular accident (Strokes)	450 cases/100,000/yr (Europe) [11] (10% of cardiovascular mortality).	Nocturia - overactive bladder (OAB) - urgency urinary incontinence (UUI) - detrusor overactivity (DO), (other patterns less frequent) [12]. 57-83% of neuro-urological symptoms at 1 month post stroke, 71-80% of spontaneous recovery at 6 months [13]. Persistence of urinary incontinence (UI) correlates with poor prognosis [14].
Dementias: Alzheimer's disease (80%), Vascular (10%), Other (10%).	6.4% of adults > 65 yrs [15].	OAB - UUI - DO 25% of incontinence in Alzheimer's disease, > 25% in other dementias: Lewy body, NPH, Binswanger, Nasu-Hakola, Pick Disease [16]. Incontinence 3 times more frequent in geriatric patients with dementia than without [17].
Parkinsonian syndrome Idiopathic Parkinson's disease (IPD): 75-80% of Parkinsonian Syndrome.	2nd most prevalent neurodegenerative disease after Alzheimer's disease. Rising prevalence of IPD with age [18].	LUTS frequency 30% at onset, 70% after 5 yrs. Storage phase symptoms: Nocturia (78%) OAB - UUI - DO [19].
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 [20]. Impaired detrusor contractility seems to be the urodynamic finding distinguishing MSA from IPD [21, 22].
Brain tumours	26.8/100,000/yr in adults (> 19 yrs), (17.9 benign, 8.9 malignant) [23].	Incontinence occurs mainly in frontal location (part of frontal syndrome or isolated in frontal location) [24].
Cerebral palsy	Cerebral palsy: 3.1-3.6/1,000 in children aged 8 yrs [25].	62% of women and 58% of men with cerebral palsy suffer from UI [26] 70% detrusor overactivity. Recurrent UTI and radiologic abnormalities in > 10% of cases [25, 26].
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 [27].	NDO and DSD (up to 95%) and detrusor underactivity (up to 83%) depending on the level of the lesion [28].
Spina bifida (SB)	Spina bifida 3-4/10,000 Lumbar and lumbosacral form are the most common (60%) [29].	Bladder function is impaired in up to 96% of SB patients [30].

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 lumboscitic episode related to disc prolapse. Incidence: approx. 5/100,000/yr More common in females > 45 yr.	26% difficulty to void and acontractile detrusor [31]. Detrusor underactivity up to (83%) [28].
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 [32].
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% [33].	Urgency/frequency +/- incontinence [34]. Hyposensitive and detrusor underactivity at later phase [34].
Disseminated central diseases		
Multiple sclerosis (MS)	Prevalence: 83/100,000 in Europe [35].	10% of MS patients present with voiding dysfunction at disease onset, 75% of patients will develop it after 10 yrs of MS [36]. DO: 86% [36]. DSD: 35% [36]. Detrusor underactivity: 25% [36].

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	Autonomic dysreflexia is a sudden and exaggerated autonomic response to various stimuli in patients with SCI or spinal dysfunction at or above level T6. It is defined as an increase in SBP ≥ 20mmHg from baseline [37]. 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	*During history taking*, the patient reports no sensation of bladder filling or desire to void [3]. *During filling cystometry*, the patient has no bladder sensation [3].
Bladder sensation, normal	*During history taking*, 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]. *During filling cystometry*, can be judged by the three 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	*During history taking*, the patient feels an early and persistent desire to void [3]. *During filling cystometry*, 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	*During history taking*, the patient reports no specific bladder sensation but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity [3]. *During filling cystometry*, may make the patient aware of bladder filling, for example, abdominal fullness or vegetative symptoms [3].
Bladder sensation, reduced	*During history taking*, the patient is aware of bladder filling but does not feel a definite desire to void [3]. *During filling cystometry*, 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 h [38].
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 [39].
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) [37].
Spinal shock	Characterised by marked reductions in spinal reflex activity below the level of injury [37].
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 20mmHg systolic or 10mmHg diastolic within 3 minutes of moving from the supine to an upright position [3, 38].
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.
Bladder pain	*During history taking*, pain that is felt suprapubically or retropubically, and usually increases with bladder filling, it may persist after voiding [3]. *During filling cystometry*, 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 [40].
Cauda equina	Injuries affecting the cauda equina and generally causing an acontractile or lower motor neuron picture affecting LUT, distal bowel and sexual function [37].
Conal	Injuries affecting the conus medullaris of the spinal cord and often causing a mixed lesion to LUT, distal bowel and sexual functions with a resultant either overactive or acontractile picture [37].
Supraconal	Injuries occurring above the conus medullaris. In general, supraconal injuries cause an overactive or upper motor neuron pattern of damage affecting LUT, distal bowel and sexual functions [37].
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	Complaint of involuntary leakage on effort or exertion, or on sneezing or coughing [3].
Urge urinary incontinence	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 change in detrusor pressure ($\Delta pdet$) during the change in bladder volume ($C=V. \Delta pdet$). It is expressed in mL/cm H_2O [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 [39].
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.
Maximum cystometric capacity	In patients with normal sensation, is 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 [39]. 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 is 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 neurologic 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, 41].
Filling rate, non-physiological	Filling rate greater than the predicted maximum filling rate [3, 41].
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 [7].

Figure 1: Patterns of lower urinary tract dysfunction following neurological disease [7]

(A) Suprapontine lesion
- **History:** predominantly storage symptoms
- **Ultrasound:** insignificant PVR urine volume
- **Urodynamics:** detrusor overactivity

Over-active / Normo-active

(B) Spinal (infrapontine–suprasacral) lesion
- **History:** both storage and voiding symptoms
- **Ultrasound:** PVR urine volume usually raised
- **Urodynamics:** detrusor overactivity, detrusor–sphincter dyssynergia

Over-active / Overactive

(C) Sacral/infrasacral lesion
- **History:** predominantly voiding symptoms
- **Ultrasound:** PVR urine volume raised
- **Urodynamics:** hypocontractile or acontractile detrusor

Under-active / Normo-active   Under-active / Underactive

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. [7] 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 [42]. This helps to prevent irreversible changes within the LUT, even in the presence of normal reflexes [43, 44]. Furthermore, urological symptoms can be the presenting feature of neurological pathology [45, 46]. Early intervention can prevent irreversible deterioration of the LUT and UUT [47].

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 [48].
- 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 [49].
- Sexual function may be impaired because of the neuro-urological condition [50].
- 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 [51, 52].
- The presence of urinary, bowel and sexual symptoms without neurological symptoms could be suggestive for an underlying neurological disease or condition.

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, incontinence and urgency episodes. Although a 24-hour bladder diary (recording should be done for three consecutive days) is reliable in women with UI [53, 54], 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. QoL is an essential aspect of the overall management of neuro-urological patients, for example when evaluating treatment related changes on a patient's QoL [55]. The type of bladder management has been shown to affect health-related QoL (HRQoL) in patients with SCI [56]. 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 [57].

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 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 [58]. In MS and SCI patients the Qualiveen [59, 60] is validated and can be used for urinary symptoms. A short form of the Qualiveen is available [59, 60] and it has been translated into various languages [61-64]. The Neurogenic Bladder Symptom Score (NBSS) has been validated in neurological patients to measure urinary symptoms and their consequences [65]. The Quality of Life scoring tool related to Bowel Management (QoL-BM) [66] can be used to assess bowel dysfunction in MS and SCI patients.

In addition, sixteen validated questionnaires evaluating QoL, that also assess urinary symptoms as a subscale or question in neuro-urological patients have been identified [67] (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 [68].

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) [58]. 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 the specific health state [69].

No evidence was found for which validated questionnaires are the most appropriate for use, since no quality criteria for the validated questionnaires have been assessed.

Table 5: Patient questionnaires

Questionnaire	Underlying neurological disorder	Bladder	Bowel	Sexual function
FAMS [70]	MS	X		X
FILMS [71]	MS	X	X	
HAQUAMS [72]	MS	X	X	X
IQOL [68]	MS, SCI	X		X
MDS [73]	MS	X	X	
MSISQ-15 / MSISQ-19 [74, 75]	MS	X	X	X
MSQLI [76]	MS	X	X	X
MSQoL-54 [77]	MS	X	X	X
MSWDQ [78]	MS	X	X	
NBSS [79]	MS, SCI, Congenital neurogenic bladder	X		
QoL-BM [66]	SCI		X	
Qualiveen/SF-Qualiveen [60, 80]	MS, SCI	X		X
RAYS [81]	MS	X		X
RHSCIR [82]	SCI	X	X	X
Fransceschini [81]	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 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 (AD) is a sudden and exaggerated autonomic response to various stimuli in patients with SCI or spinal dysfunction. It generally manifests at or above level T6. The stimulus can be distended bladder or bowel. For example, iatrogenic stimuli during cystoscopy or urodynamics can trigger AD [1]. It can also be secondary to sexual stimulation or a noxious stimulus, e.g. infected toe nail or pressure sore. AD is defined by an increase in systolic blood pressure ≥ 20mmHg from baseline [37] and can have life-threatening consequences if not properly managed [83].

Figure 2: Lumbosacral dermatomes, cutaneous nerves, and reflexes [7]
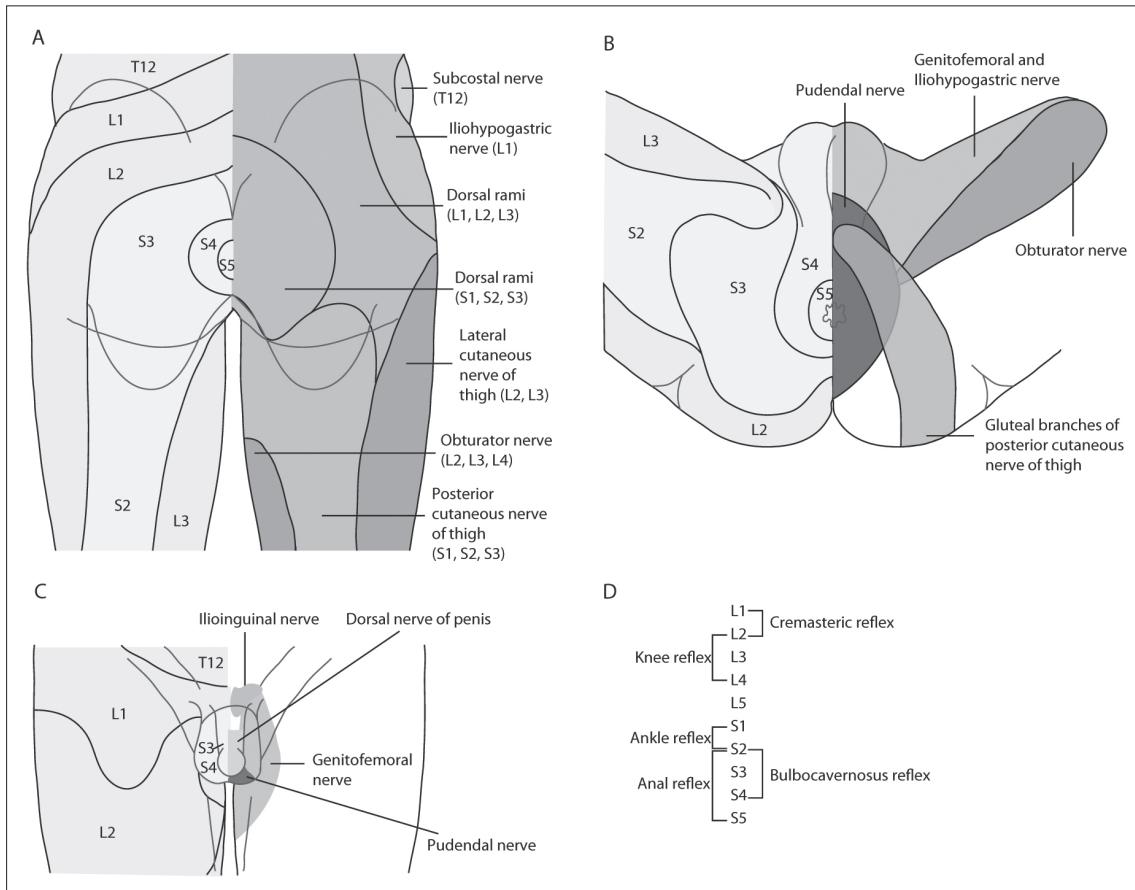
The physical examination includes testing sensations and reflexes mediated through the lower spinal cord. Abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of lesion. Distribution of dermatomes (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 [84] (B), male external genitalia [85] (C) and root values of lower spinal cord reflexes (D). Parts A–C adapted from Standring [86], 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
An extensive general history is mandatory, concentrating on past and present symptoms including urinary, sexual, bowel, and neurological functions.	4	A
Special attention should be paid to the possible existence of alarm signs, e.g. pain, infection, haematuria, fever, that warrant further specific diagnosis.	4	A
A specific history should be taken for each of the four mentioned functions.	4	A
Quality of life should be assessed when evaluating and treating the neuro-urological patient.	2a	B
The available validated tools are the Qualiveen and I-QoL for urinary symptoms and the QoL-BM for bowel dysfunction for MS and SCI patients. In addition, generic, (SF-36 or KHQ) questionnaires can be used.	1a	A
Physical examination		
Individual patient disabilities should be acknowledged in planning further investigations.	4	A
The neurological status should be described as completely as possible. Sensations and reflexes in the urogenital area must all be tested.	4	A
The anal sphincter and pelvic floor functions must be tested.	4	A
Urinalysis, blood chemistry, bladder diary, residual and free flowmetry, incontinence quantification and urinary tract imaging should be performed.	4	A

** All grade A recommendations are based on panel consensus; I-QoL = incontinence quality of life,
MS = multiple sclerosis and SCI = spinal cord injury..*

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 these patients, invasive urodynamic investigation is even more provocative 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 [87].

In patients at risk for AD, it is advisable to measure blood pressure during the urodynamic study [88]. 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 ICS technical recommendations and standards [1, 89].

3.3.7.2   Urodynamic tests
Free uroflowmetry and assessment of residual urine: This 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 2-3 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 is the only method for quantifying the filling function (undertaken at a very slow rate ~20 mL/min). 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, as fast filling and room-temperature saline are provocative. Possible pathological findings include DO, low bladder compliance, abnormal bladder sensations, incontinence, and an incompetent or relaxing urethra.

Detrusor leak point pressure (DLPP) [90]: This appears to have no use as a diagnostic tool. Some positive findings have been reported [91, 92], but sensitivity is too low to estimate the risk to the UUT or for secondary bladder damage [93, 94].

Pressure flow study: This 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. LUT function must be recorded during the voiding phase. Possible pathological findings include detrusor underactivity, BOO, DSD, a high urethral resistance, and residual urine.

Most types of obstruction caused by neuro-urological disorders are due to DSD [95, 96], non-relaxing urethra, or non-relaxing bladder neck [97, 98]. Pressure-flow analysis mostly 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): This 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 [99].

Urethral pressure measurement: This has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings [100].

Video-urodynamics: This is the combination of filling cystometry and pressure flow study with imaging. It is the gold standard 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 UUT [101].

Ambulatory urodynamics: This is the functional investigation of the urinary tract, which uses the predominantly 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 [101].

Provocative tests during urodynamics: LUT 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 (UMNL/LMNL) [102, 103]. 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 [104].

Previously, a positive bethanechol test [105] (detrusor contraction > 25 cm H_2O) 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 [106], 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 [107]:
- 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
The recording of a bladder diary is advisable.	3	A
Non-invasive testing is mandatory before invasive urodynamics is planned.	4	A
Urodynamic investigation is necessary to detect and specify lower urinary tract (dys-) function and same session repeat measurement is crucial in clinical decision making.	1b	A
Video-urodynamics is the gold standard for invasive urodynamics in neuro-urological patients. If this is not available, then a filling cystometry continuing into a pressure flow study should be performed.	4	A
A physiological filling rate and body-warm saline should be used.	4	A
Specific uro-neurophysiological tests are elective procedures.	4	C

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 [108]. Patients with SCI or spina bifida have a substantially higher risk of developing renal failure compared with patients with slowly progressive non-traumatic neurological disorders, such as multiple sclerosis and Parkinson's disease [109].

Caregivers must be informed of this condition 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 [110].

3.4   Disease management
3.4.1   Introduction
The primary aims for treatment of neuro-urological symptoms and their priorities are [111, 112]:
- 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 [112].

Renal failure is the main mortality factor in SCI patients who survive the trauma [113, 114]. Keeping the detrusor pressure during both the filling and voiding phases within safe limits significantly reduces the mortality from urological causes in these patients [115-117] and has consequently become the golden rule in the treatment of patients with neuro-urological symptoms [111, 112].

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 [111]. Reduction of the detrusor pressure contributes to urinary continence, and consequently to social rehabilitation and QoL. It is also pivotal in preventing UTI [118, 119]. Complete continence can however not 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 [120, 121]. 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 [122, 123]. Their use should therefore be discouraged unless urodynamics show that the intravesical pressure remains within safe limits [124].

Long-term complications are unavoidable for both methods of bladder emptying [121]. The already weak pelvic floor function may be further impaired, thus introducing or exacerbating already existing stress urinary incontinence (SUI) [123].

Triggered reflex voiding: Stimulation of the sacral or lumbar dermatomes in patients with UMNL can elicit a reflex detrusor contraction [123]. The risk of high pressure voiding is present and interventions to decrease outlet resistance may be necessary [125]. Triggering can induce AD, especially in patients with high level SCI (at or above Th 6) [126]. 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 [123, 127-129].

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 [112]. Condom catheters with urine collection devices are a practical method for men [112]. The infection risk must be closely observed [112]. 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 [112, 130]. The first mechanism is affected by activation of efferent nerve fibres, and the latter ones are produced by activation of afferent fibres [93]. Electrical stimulation of the pudendal nerve afferents strongly inhibits the micturition reflex and detrusor contraction [131]. This stimulation might then support the restoration of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level [112, 132, 133]. 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: Early data suggest 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 [5, 134, 135].

Peripheral electrostimulation combined with pelvic floor muscle training/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 [136]. Furthermore, this treatment combination is significantly superior to electrostimulation alone. Biofeedback can be used for supporting the alleviation of neuro-urological symptoms [137].

Intravesical electrostimulation: Intravesical electrostimulation can increase bladder capacity and improve bladder compliance and bladder filling sensation in patients with incomplete SCI or MMC [138]. In patients with neurogenic detrusor underactivity, intravesical electrostimulation may also improve voiding and reduce residual volume [139, 140].

Repetitive transcranial magnetic stimulation: Although improvement of neuro-urological symptoms has been described in PD and MS patients, this technique is still under investigation [141, 142].

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 SCI with a suprasacral lesion or MS [123, 143-147].

3.4.2.3.1   Drugs for storage symptoms
Antimuscarinic drugs: They are the first-line choice for treating neurogenic detrusor overactivity
(NDO), increasing bladder capacity and reducing episodes of UI secondary to NDO by the inhibition of
parasympathetic pathways [124, 148-154]. Antimuscarinic drugs have been used for many years to treat
patients with NDO [151, 152, 155], and the responses of individual patients to antimuscarinic treatment are
variable. Only a recent meta-analysis has confirmed the clinical and urodynamic efficacy of antimuscarinic
therapy compared to placebo in adult NDO [152].

Higher doses or a combination of antimuscarinic agents may be an option to maximise outcomes in
neurological patients [143, 145, 153, 154, 156, 157]. However, these drugs have a high incidence of adverse
events, which may lead to early discontinuation of therapy [152, 153, 156].

Choice of antimuscarinic agent: Oxybutynin [124, 145, 148, 151-154, 158] trospium [152, 156, 159], tolterodine
[160-162] and propiverine [148, 152, 163-166] are established, effective and well tolerated treatments even in
long-term use [151, 152, 167, 168]. Darifenacin [168] and solifenacin have been evaluated in NDO secondary to
SCI and MS [152, 169-172] with results similar to other antimuscarinic drugs. A study using solifenacin in NDO
due to Parkinson's disease has recently been completed [173]. 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.

Side effects: Controlled release antimuscarinics have some minor side effects, e.g. dry mouth [174]. It has been
suggested that different ways of administration may help to reduce side effects. In a selected group of patients,
transdermal oxybutynin was found to be well tolerated and effective [175].

Other agents
Beta-3-adrenergic receptor agonist: Have recently been introduced and evaluated in OAB, but clinical
experience in neuro-urological patients is limited [176]. Studies on safety and effectiveness in NDO are ongoing
[177]. Depending on the results of this studies, combined therapy with antimuscarinics may be an attractive
option [178].

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
[179]. Only preclinical studies have documented the potential benefits of cannabinoid agonists on improving
detrusor contractility when administered intravesically [180, 181]. Conversely, a randomised controlled study
on the use of oromucosal nabixinols (an endocannabinoid modulator), did not report any significant reduction
of incontinence episodes in MS patients, although a statistically significant improvement in frequency, urgency
and nocturia was documented [182].

Decreasing bladder outlet resistance: α-blockers (e.g. tamsulosin and naftopidil) seem to be effective for
decreasing bladder outlet resistance, postvoid residual and autonomic dysreflexia [183].

Increasing bladder outlet resistance: Several drugs have shown efficacy in selected cases of mild stress urinary
incontinence (SUI), but there are no high-level evidence studies in neurological patients [124].

3.4.2.4   *Recommendations for drug treatments*

Recommendations	LE	GR
For NDO, antimuscarinic therapy is the recommended first-line medical treatment.	1a	A
Alternative routes of administration (i.e., transdermal or intravesical) of antimuscarinic agents may be used.	2	A
Outcomes for NDO may be maximised by considering a combination of antimuscarinic agents.	3	B
To decrease bladder outlet resistance, alpha-blockers could be prescribed.	1b	A
For underactive detrusor, parasympathomimetics should not be prescribed.	1a	A
In neurogenic stress urinary incontinence, drug treatment should not be prescribed.	4	A

NDO = neurogenic detrusor overactivity

3.4.2.5   Minimally invasive treatment

3.4.2.5.1   Catheterisation

Intermittent self- or third-party catheterisation [184, 185] is the preferred management for neuro-urological patients who cannot effectively empty their bladders [111, 112].

Sterile IC, as originally proposed by Guttmann and Frankel [184], significantly reduces the risk of UTI and bacteriuria [112, 186, 187], compared with clean IC introduced by Lapides *et al.* [185]. However, it has not yet been established whether incidence of UTI, other complications, or user satisfaction are affected by sterile or clean technique, coated or uncoated catheters or by any other strategy. Sterile IC cannot be considered a routine procedure [112, 187].

Aseptic IC is an alternative to sterile IC [188].

Contributing factors to contamination are insufficient patient education and the inherently greater risk of UTI in neuro-urological patients [112, 189-192]. The average frequency of catheterisations per day is 4-6 times [193] and the catheter size most often used is between 12-16 Fr. In aseptic IC, an optimum frequency of 5 times showed a reduction of UTI [193]. 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 [112, 194-202]. Both procedures should therefore be avoided when possible. Silicone catheters are preferred because they are less susceptible to encrustation and because of the high incidence of latex allergy in the neuro-urological patient population [203].

3.4.2.5.2   Recommendations for catheterisation

Recommendations	LE	GR
Intermittent catheterisation - whenever possible aseptic technique - should be used as a standard treatment for patients who are unable to empty their bladder.	3	A
Patients must be well instructed in the technique and risks of IC.	3	A
The catheter size should be 12-16 Fr.	4	B
Whenever possible, indwelling transurethral and suprapubic catheterisation should be avoided.	3	A

IC = intermittent catheterisation

3.4.2.5.3   Intravesical drug treatment

To reduce DO, antimuscarinics can also be administered intravesically [204-208]. 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 [208]. This approach may reduce adverse effects because the antimuscarinic drug is metabolised differently [205] and a greater amount is sequestered in the bladder, even more than with electromotive administration [204].

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 [209-211]. 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 [210]. 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

BTX-A causes a long-lasting but reversible chemical denervation that lasts for about 9 months [212, 213]. The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. BTX-A has been proven effective in patients with neuro-urological disorders due to MS or SCI in phase III RCTs [214-216] and systematic reviews [217, 218]. Repeated injections seem to be possible without loss of efficacy [212, 216, 219]. The most frequent side effects are UTIs and elevated PVR [215, 216]. IC may become necessary. Rare but severe adverse events include autonomic dysreflexia and respiratory problems. Generalised muscular weakness may occur [212, 215, 219].

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).

BTX-A: This can be used to treat detrusor sphincter dyssynergia 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 [220-222]. However, a recent Cochrane report concluded that because of limited evidence future RCTs assessing the effectiveness of BTX injections also need to address the uncertainty about the optimal dose and mode of injection [223]. In addition, this therapy is not licensed.

Balloon dilatation: Favourable immediate results were reported [224], but there are no further reports since 1994 so 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 [111, 112, 214]. Different techniques are used, and laser treatment appears to be advantageous [225, 226]. Sphincterotomy needs to be repeated at regular intervals in many patients [227], but it is efficient and does not cause severe adverse effects [111, 224]. Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered [228].

Bladder neck incision: This is indicated only for secondary changes at the bladder neck (fibrosis) [111, 225]. This procedure is not recommended in patients with detrusor hypertrophy, which causes thickening of the bladder neck [111].

Stents: Implantation of urethral stents results in continence being dependent on adequate closure of the bladder neck [112]. The results are comparable with sphincterotomy and the stenting procedure has a shorter duration of surgery and hospital stay [229, 230]. However, the costs [111], possible complications and re-interventions [231, 232] are limiting factors in its use [233-236].

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 [112, 237, 238].

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 [239].

3.4.2.5.6 Recommendations for minimal invasive treatment*

Recommendations	LE	GR
Botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity in MS or SCI.	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
MS = multiple sclerosis; SCI = spinal cord injury.

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 [112].

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 [112, 240-245]. There is growing evidence that synthetic slings can be used effectively with acceptable medium to long-term results and minimal morbidity in neuropathic patients [246, 247]. In men, both autologous and synthetic slings may also be an alternative [246-250].

Artificial urinary sphincter: This device was introduced by Light and Scott [251] for patients with neuro-urological disorders [112]. It has stood the test of time and acceptable long-term outcomes can be obtained [252-257].

Functional sphincter augmentation: By transposing the gracilis muscle to the bladder neck [258] or proximal urethra [259], there is a possibility to create a functional autologous sphincter by electrical stimulation [258-260]. This opens the possibility of restoring control over the urethral closure.

Bladder neck and urethra reconstruction: The classical Young-Dees-Leadbetter procedure [261] for bladder neck reconstruction in children with bladder exstrophy, and Kropp urethra lengthening [262] improved by Salle [263], are established methods to restore continence provided that IC is practiced and/or bladder augmentation is performed [112, 264].

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 detrusor overactivity [265-267], but nowadays, it is used mostly as an adjuvant to sacral anterior root stimulation (SARS) [268-272]. Alternatives to rhizotomy are sought in this treatment combination [273-275].

SARS is aimed at producing detrusor contraction. The technique was developed by Brindley [276] and is only applicable to complete lesions above the implant location, because 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 [269, 277, 278]. By changing the stimulation parameters, this method can also induce defecation or erection.

Sacral neuromodulation (SNM) [279] might be effective and safe for treating neuro-urological symptoms but there is a lack of RCTs and it is unclear which neurological patient is most suitable [280-282].

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 [283] and latissimus dorsi [284] have been used successfully in patients with neuro-urological symptoms [285, 286].

3.4.3.4   Bladder augmentation
The aim of auto-augmentation (detrusor myectomy) is to reduce detrusor overactivity 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 [111, 112, 287-293].

Replacing or expanding the bladder by intestine or other passive expandable coverage will improve bladder compliance and at least reduce the pressure effect of detrusor overactivity [294, 295]. Inherent complications associated with these procedures are: recurrent infection, stone formation, perforation or diverticula, possible malignant changes, and for intestine metabolic abnormality, mucus production and impaired bowel function [112, 296-298]. 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.

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 [289, 299-307]. Bladder substitution to create a low-pressure reservoir is indicated in patients with a severely thick and fibrotic bladder wall [112]. IC may become necessary after this procedure.

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 [112].

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 [112, 308-320]. For cosmetic reasons,

the umbilicus is often used for the stoma site [315, 318, 319, 321-323].

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 [112]. An ileal segment is used for the deviation in most cases [112, 324-327].

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 [112]. The patient must be carefully counselled and must comply meticulously with the instructions [112]. Successful undiversion can then be performed [328].

3.4.3.6 Recommendations for surgical treatment

Recommendations	LE	GR
In order to treat refractory neurogenic detrusor overactivity, bladder augmentation is recommended. Detrusor myectomy is an acceptable alternative in highly selected cases.	3	A
In female patients with neurogenic stress urinary incontinence who are able to self-catheterise, placement of an autologous urethral sling should be used.	4	B
In male patients with neurogenic stress urinary incontinence, artificial urinary sphincter should be used.	3	A

3.5 Urinary tract infection in neuro-urological patients

3.5.1 Epidemiology, aetiology and pathophysiology

Urinary tract infection (UTI) is the onset of signs and/or symptoms accompanied by laboratory findings of a UTI (bacteriuria, leukocyturia and positive urine culture) [321]. 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 $> 10^2$ colony-forming units 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 [321].

The pathogenesis of UTI in neuro-urological patients is multifactorial. Several etiological factors have been described: altered intrinsic defence mechanisms, impaired washout and catheterisation [329]. 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% [330]. Sphincterotomy and condom catheter drainage has a 57% prevalence [331]. Asymptomatic bacteria should not be routinely screened for in this population [332].

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 autonomic dysreflexia, may develop or worsen due to a UTI [333]. 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 autonomic dysreflexia [333, 334].

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 [335, 336]. As bacterial strains and resistance patterns in persons with neuro-urological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory [337].

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 [338]. UTI 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 5-7 day course of antibiotic treatment is advised, that can be extended up to 14 days according to the extent of the infection [338]. The choice of the 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 autonomic dysreflexia), the choice of treatment should be based on local and individual resistance profiles [339].

3.5.3.1 Recurrent UTI
Recurrent UTI in patients with neuro-urological disorders may indicate a 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 detrusor overactivity by BTX-A injection in the detrusor [340], and the removal of bladder stones or other direct supporting factors, especially indwelling catheters, as early as possible, are mandatory [337].

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 is associated with a lower rate of UTI in a recent meta-analysis [341]. Bladder irrigation has not been proven effective [342].

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 [343]. Methenamine hippurate is not effective in individuals with neuro-urological symptoms [344]. There is no sufficient evidence to support the use of L-methionine for urine acidification to prevent recurrent UTI [345]. There is only weak evidence that oral immunotherapy reduces bacteriuria in patients with SCI, and no evidence that recurrent UTIs are reduced [346]. Low-dose, long-term, antibiotic prophylaxis cannot reduce UTI frequency, but increases bacterial resistance and is therefore not recommended [338].

A newly proposed application scheme of antibiotic substances for antibiotic prophylaxis provided positive results, but the results of this trial need to be confirmed in further studies [347]. 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 [348], 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 [349]. 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
Asymptomatic bacteriuria in patients with neuro-urological disorders should neither be screened for nor be treated.	4	A
The use of long-term antibiotics for recurrent UTI should be avoided.	2a	A
In patients with recurrent UTI, treatment of neuro-urological symptoms should be optimised and foreign bodies (e.g. stones, indwelling catheters) should be removed 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

UTI = urinary tract infection.

3.6   Sexual (dys)function and fertility
These Guidelines specifically focus on sexual dysfunction and infertility in patients with a neurological disease [350]. Non-neurogenic, male sexual dysfunction and infertility are covered in separate EAU Guidelines [351, 352]. 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 [353]. Adopting a systematic approach, such as the PLISSIT model (Permission, Limited Information, Specific Suggestions and Intensive Therapy) [354], provides a framework for counselling and treatment involving a stepwise approach to the management of neurogenic sexual dysfunction.

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) [350, 355]. In SCI patients, tadalafil, vardenafil and sildenafil have all improved retrograde ejaculation and improved erectile function and satisfaction on IIEF-15. Tadalafil 10mg was shown to be more effective than sildenafil 50mg. All currently available PDE5Is appear to be effective and safe, although there are no high-evidence level studies in neuro-urological patients investigating efficacy and side effects across different PDE5Is, dosages and formulations [356].

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 Parkinson's disease normal erectile function was described in over half of the patients using sildenafil 100mg and a significant improvement in IIEF 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 [357, 358], most commonly headache and flushing [355]. In addition, PDE5Is may induce relevant hypotension in patients with tetraplegia/ high-level paraplegia and multiple system atrophy [357, 358]. 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 autonomic dysreflexia, they must be counselled that PDE5Is are contraindicated when using nitrate medication.

3.6.1.2 Drug therapy other than PDE5I

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 [359]. Sublingual apomorphine was shown to have poor results on ED in SCI patients and side-effects in half of the patients [360]. In Parkinson's disease pergolide mesylate showed a significant improvement in IIEF-15 scores up to 12 months follow-up [361].

3.6.1.3 Mechanical devices

Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular [362-366].

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 [367-373] 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 [357]. Intraurethral alprostadil application is an alternative but a less effective route of administration [373, 374].

3.6.1.5 Sacral neuromodulation

Sacral neuromodulation for LUT dysfunction may improve sexual function but high-evidence level studies are lacking [355].

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 [355]. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type [375-377].

3.6.1.7 Recommendations for erectile dysfunction

Recommendations	LE	GR
In neurogenic ED, oral PDE5Is are the recommended first-line medical treatment.	1b	A
In neurogenic ED, intracavernous injections of vasoactive drugs (alone or in combination) are the recommended second-line medical treatment.	3	A
In neurogenic ED, mechanical devices such as vacuum devices and rings can be effective and may be offered to patients.	3	B
In neurogenic ED, penile prostheses should be reserved for selected patients.	4	B

ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors.

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, spina bifida, MS and SCI [378]. ED is managed as described previously. Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck, including imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine [378]. The use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation [379]. If antegrade ejaculation is not achieved, the harvest of semen from the urine may be considered [380].

Prostatic massage is safe and easy to use for obtaining semen in men with lesions above Th 10 [381]. In several patients, vibrostimulation or transrectal electroejaculation are needed for sperm retrieval [373, 378, 382, 383]. Semen retrieval is more likely with vibrostimulation in men with lesions above Th 10 [384-386]. In men with SCI, especially at or above Th 6, AD might occur during sexual activity and ejaculation [387, 388]; 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 [389].

In men with MS, use of disease modifying drugs during the conception phase, has not been associated with altered pregnancy outcomes [390].

Surgical procedures, such as, microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE), may be used if vibrostimulation and electroejaculation are not successful [391, 392]. 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 [393-395].

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 [396].
*   In SCI patients sperm quality decreases at the early post traumatic phase demonstrating lower spermatozoid vitality (necrospermia) reduced motility (asthenospermia) and leucospermia [391].
*   Long-term valproate treatment for epilepsy negatively influences sperm count and motility [397].
*   Vibrostimulation produces samples with better sperm motility than electrostimulation [398, 399].
*   Electroejaculation with interrupted current produces better sperm motility than continuous current [400].
*   Freezing of sperm is unlikely to improve fertility rates in men with SCI [401].

3.6.2.2 Recommendations for male fertility

Recommendations	LE	GR
In men with SCI, vibrostimulation and transrectal electroejaculation are effective methods of sperm retrieval.	3	B
In men with SCI; MESA, TESE or ICSI may be used after failed vibrostimulation and/or transrectal electroejaculation.	3	B
In men with SCI, especially at or above Th 6, it is essential to counsel patients at risk and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	3	A

ICSI = intracytoplasmic sperm injection; MESA = microsurgical epididymal sperm aspiration; SCI = spinal cord injury; TESE = testicular sperm extraction.

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 [402-404]. Although sexual dysfunction is very common in women with MS, it is still often overlooked by medical professionals [405, 406].

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 [402, 407-409].

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 [410]. Although good evidence exists that psychological interventions are effective in the treatment of female hypoactive sexual desire disorder and female orgasmic disorder [411], 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 [412-414].

Sacral neuromodulation for LUT dysfunction may improve sexual function but high-evidence studies are lacking [410].

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 [412, 415, 416].

3.6.3.1 Recommendation for female sexuality

Recommendation	LE	GR
There is no effective medical therapy for the treatment of neurogenic sexual dysfunction in women.	4	A

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 [417].

Although it seems that the reproductive capacity of women with SCI is only temporarily affected by SCI with cessation of menstruation for approximately 6 months after SCI [418], 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 [419].

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 [420, 421]. Obstetric outcomes include higher rates of Caesarean sections and an increased incidence of low birth-weight babies [419].

Epidural anaesthesia is chosen and effective for most patients with AD during labour and delivery [422, 423].

There is very little published data on women's experience of the menopause following SCI [424].
Women with MS who plan a pregnancy should evaluate their current drug treatment with their treating physician [425]. Clinical management should be individualised to optimize both the mother's reproductive outcomes and MS course [426].

3.6.4.1   Recommendation for female fertility

Recommendation	LE	GR
In women with a neurological disease, the management of fertility, pregnancy and delivery requires a multidisciplinary approach tailored to individual patient's needs and preferences.	4	A

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 [110].

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 1-2 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 6 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-evidence level studies on this topic and every recommendation must be viewed critically in the individual neuro-urological patient [110].

3.7.2   Recommendations for follow-up

Recommendations	LE	GR
In high-risk patients, the upper urinary tract should be assessed at regular intervals.	4	A
In high-risk patients, physical examination, and urine laboratory should take place every year.	4	A
Any significant clinical changes should instigate further, specialised, investigation.	4	A
Urodynamic investigation is a mandatory baseline diagnostic and in high-risk patients, should be done at regular intervals.	3	A

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 therapeutical options, each with its own pros and cons. Notwithstanding the success of any therapy embarked upon, a 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.

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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

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1. INTRODUCTION

1.1 Aim

These guidelines include 4 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). ED 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. 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 4 hours and is beyond, or is unrelated to, sexual interest or stimulation [3] (LE: 4). Overall, erections lasting up to 4 hours are by consensus defined as 'prolonged' (LE: 4). 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) [4, 5]. In men with sickle cell disease, the prevalence of priapism is up to 3.6% in men < 18 years of age [6] increasing up to 42% in men $\geq$ 18 years of age [7-10].

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.

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 to "EAU Guidelines on Male Sexual Dysfunction" [11]. In 2011 the Panel decided to develop new guidelines addressing Penile Curvature, which resulted in a new publication in 2012 [12]. In 2014 a guideline on Priapism was completed [13].

In this 2016 edition, the phrasing of some recommendations has been updated including some minor corrections. This edition also merged the previous EAU guidelines for ED, PE, penile curvature and priapism into one guideline.

1.3 Available Publications

Alongside several scientific summaries published in the EAU scientific journal, European Urology [14-18], 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 for personal use 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

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. 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.

For the topics of ED and PE, a systemic literature search was performed in 2015 by the panel members. The MedLine database was searched using the major Medical Subject Headings (MeSH) terms "erectile dysfunction", "sexual dysfunction" "ejaculation". All articles published between January 2009 (previous update) and October 2014 were considered for review. For Premature Ejaculation the MedLine search was supplemented by the term "premature ejaculation" in all search fields, for the 2015 print, covering a time frame up to October 2014. The Panel also identified critical problems and knowledge gaps, setting priorities for future clinical research.

For PE, a systematic literature search of the Medline database was also performed in 2015. The controlled vocabulary of the Medical Subject Headings (MeSH) database uses the specific term 'penile induration' for Peyronie's disease. There is no specific MeSH term for congenital penile curvature. In order to identify relevant articles, the search included the MeSH terms 'congenital abnormalities', 'penis abnormalities' and 'male' as well as the free text term 'congenital penile curvature'. The search included all relevant articles published up to July 2014. A total of 199 articles were identified for congenital penile curvature while this number was 1,806 for Peyronie's disease. The panel reviewed and selected the articles with the highest evidence available. However, in several subtopics only articles with low LE were available and discussed accordingly.

Finally, the guidelines on Priapism are based on a systematic literature search performed by the Panel members in 2015. The MedLine database was searched using the major Medical Subject Headings term 'priapism' with search cut-off date of October 2014. This search yielded 1,688 articles (192 review articles, 485 original articles and 911 case reports). The Panel also identified critical problems and knowledge gaps, enabling priorities to be established for future clinical research.

2.1   Review
This document was subject to peer review prior to publication in 2015. The decision to 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.

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 [19]. ED is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [20]. ED may affect physical and psychosocial health and may have a significant impact on the quality of life (QoL) of sufferers and their partners [21-23]. There is increasing evidence that ED can be an early manifestation of coronary artery and peripheral vascular disease. ED should not be regarded only as a QoL issue, but also as a potential warning sign of cardiovascular disease (CVD) [24-26].

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) [21] 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% [27]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [28] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [29]. 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 [30]. 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

ED shares both unmodifiable and modifiable common risk factors with CVD (e.g., obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, lack of exercise, and smoking) [23, 31, 32]. In this context, men with mild ED have similar risk factors to those of a general ED clinical trial population [33]. Thus, mild ED emerged as an important indicator of risk for associated underlying disease (CVDs) [33]. A number of studies have shown some evidence that lifestyle modification [25, 34] and pharmacotherapy [34, 35] for cardiovascular 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 [26].

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 [36]. 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 an 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% [37].

3.1.1.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 1) [19].

Table 1: Pathophysiology of ED

Vasculogenic
• Cardiovascular disease (hypertension, coronary artery disease, peripheral vasculopathy, etc.)
• Diabetes mellitus
• Hyperlipidaemia
• Smoking
• Major pelvic surgery (RP) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
Central causes
• Degenerative disorders (multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
• Spinal cord trauma or diseases
• Stroke
• Central nervous system tumours
Peripheral causes
• Type 1 and 2 diabetes mellitus
• Chronic renal failure
• Polyneuropathy
• Surgery (major surgery of pelvis/retroperitoneum, radical prostatectomy (RP), colorectal surgery, etc.)
• 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 10 years. 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 [38, 39]. Research has shown that 25-75% of men experience post-operative ED [40]. 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 [41], without significant differences between laparoscopic RP and RARP. However, more controlled prospective studies are necessary to determine the actual superiority of RARP in terms of post-operative ED rates [42]. 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 [38, 39].

Pre-operative potency is a major factor associated with the recovery of erectile function after surgery. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [38, 39]. Overall, the temporal 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). 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 [38, 40].

ED is also a common sequela after external beam radiotherapy and brachytherapy for PCa [43, 44]. The mechanisms contributing to ED after prostate irradiation involve injury to the neurovascular bundles, penile vasculature, and cavernosal structural tissue [43, 44]. 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 [45, 46].

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*
ED 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 [47, 48]. In this context, taking a comprehensive medical history may reveal one of the many common disorders associated with ED [47, 48]. 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 [47, 49]. Validated psychometric questionnaires, such as the International Index for Erectile Function (IIEF) [50] or its short version the Sexual Health Inventory for Men (SHIM), 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 [51]. In cases of clinical depression, the use of a 2-question scale for depression is recommended in the every day 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?" [52]. 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. For this specific purpose, screening questionnaires, such as the International Prostate Symptom Score may be utilised [53].

3.1.3.1.2   Physical examination
Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular, and neurological systems [54, 55]. 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 3-6 months.

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 bioavailable or calculated-free testosterone may be needed to corroborate total testosterone measurements. However, the threshold of testosterone to maintain an erection is low and ED is usually a symptom of more severe cases of hypogonadism [31, 56-58]. For levels > 8 nmol/l the relationship between circulating testosterone and sexual functioning is very low [31, 56-58]. Additional laboratory tests may be considered in selected patients (e.g., prostate-specific antigen (PSA) [59]; prolactin, and luteinising hormone [60]. 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 [55].

Figure 1: Minimal diagnostic evaluation (basic work-up) in patients with ED

Patient with ED (self-reported)

↓

Medical and psychosexual history (use of validated instruments, e.g. IIEF)

↓

| Identify other than ED sexual problems | Identify common causes of ED | Identify reversible risk factors for ED | Assess psychosocial status |

↓

Focused physical examination

↓

| Penile deformities | Prostatic disease | Signs of hypogonadism | Cardiovascular and neurological status |

↓

Laboratory tests

↓

| Glucose-lipid profile (if not assessed in the last 12 months) | Total testosterone (morning sample) If indicated, bio-available or free testosterone |

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 [61] and women [62]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [63, 64]. ED significantly increases the risk of CVD, coronary heart disease, stroke, and all cause mortality, and the increase is probably independent of conventional cardiovascular risk factors [24, 25, 65].

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 [24]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [66-68]. 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 [35].

Table 2: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus [67, 68])

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 ED (based on 3rd Princeton Consensus) [68]
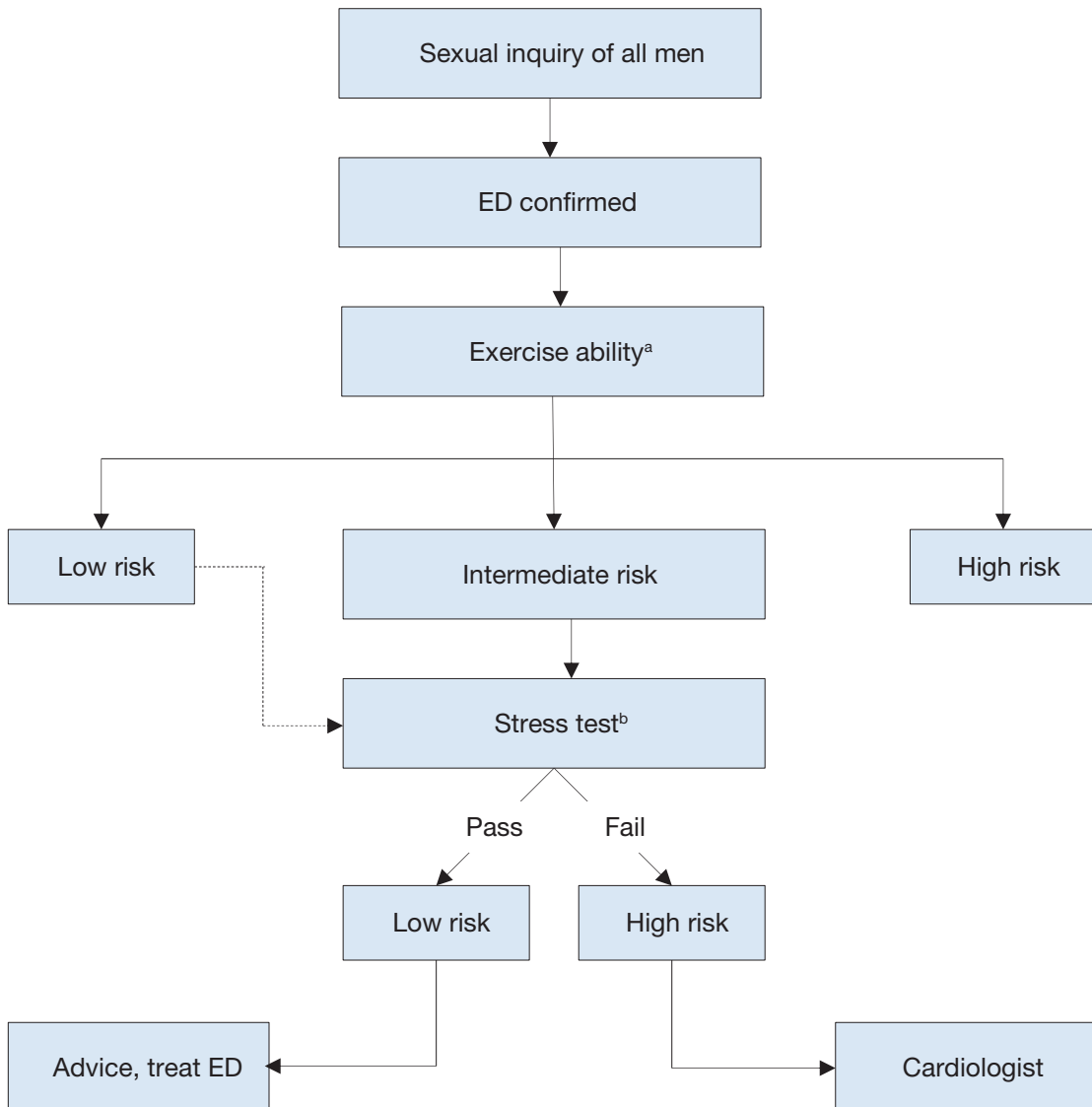
[a] Sexual activity is equivalent to walking 1 mile on the flat in 20 min or briskly climbing two flights of stairs in 10 s.
[b] Sexual activity is equivalent to 4 min of the Bruce treadmill protocol.

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 ≥ 10 min [69].

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 10 min after the intracavernous injection and lasts for 30 min [70]. 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 [71]. Further vascular investigation is unnecessary when a Duplex 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 [72].

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 [30], 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 [73]. Patient and partner education is an essential part of ED management [73, 74].

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 vascular surgery.
Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital 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

NTPR using Rigiscan®
Vascular studies
- Intracavernous vasoactive drug injection
- Penile Dynamic Duplex Ultrasonography
- Penile Dynamic Infusion Cavernosometry and Cavernosography
- 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 ED 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 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

ED = erectile dysfunction.

3.1.4   Disease management
3.1.4.1   Treatment options

ED may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors. 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, for instance, 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. 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 [57, 60]), 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 [73]. 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 [26, 75].

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 [38]. 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 the first-line therapy in patients who have undergone nerve-sparing (NS) surgery regardless of the surgical technique used [38, 39]. 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-operative erectile function [38, 39, 41]. 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 [38, 76]. Early use of high-dose sildenafil after RP has been suggested to be associated with preservation of smooth muscle within the corpora cavernosa [77]. 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 [78].

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 [38, 79]. Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study in North America [38, 80]. 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 [38, 81]. Moreover, a randomised, double-blind, double-dummy trial in men ≤ 68 yr 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 [82]. Tadalafil was most effective on 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 [82]. Unassisted erectile function was not improved after cessation of active therapy for 9 months [82]. Moreover, data suggested that the use of tadalafil once daily can significantly shorten the time to erectile function recovery post-NSRP compared to placebo [83].

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. 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 [84]. 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 12 weeks showed significantly greater increases in SEP2 (sexual encounter profile) and SEP3 and change in mean IIEF erectile function domain score with 100 and 200 mg avanafil vs. placebo (p < 0.01) [85]. Following dosing with avanafil 36.4% (28 of 77) of sexual attempts (SEP3) at 15 minutes or less were successful vs. 4.5% (2 of 44) for placebo (p < 0.01) [85].

Historically, the treatment options for post-operative ED have included intracavernous injections [38, 86], urethral microsuppository [38, 87], vacuum device therapy [38, 88], and penile implants [38, 89, 90]. 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).

Figure 3: Treatment algorithm for erectile dysfunction

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                    ┌─────────────────────────────────┐
                    │  Treatment of erectile dysfunction│
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          ┌───────────────┘         │         └───────────────┐
          ▼                         ▼                         ▼
┌──────────────────┐   ┌──────────────────┐   ┌──────────────────┐
│ Identify and treat│   │ Lifestyle changes │   │ Provide education │
│ 'curable' causes of│   │ and risk factor   │   │ and counselling to│
│ erectile dysfunction│  │ modification      │   │ patients and partners│
└──────────────────┘   └──────────────────┘   └──────────────────┘
                                   │
                    ┌──────────────────────────────────────────┐
                    │ Identify patient needs and expectations    │
                    │ Shared decision-making                     │
                    │ Offer conjoint psychosocial and medical treatment│
                    └──────────────────────────────────────────┘
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                          ▼                         ▼
               ┌──────────────┐          ┌──────────────────────┐
               │    PDE5      │◄────────►│ Intracavernous injections│
               │  inhibitors  │          │ Vacuum devices         │
               └──────────────┘          │ Intraurethral/topical  │
                                         │ alprostadil            │
                                         └──────────────────────┘
                                   │
                    ┌──────────────────────────────┐
                    │ Assess therapeutic outcome:    │
                    │ • Erectile response            │
                    │ • Side-effects                 │
                    │ • Treatment satisfaction       │
                    └──────────────────────────────┘
                                   │
                    ┌──────────────────────────────┐
                    │ Inadequate treatment outcome   │
                    └──────────────────────────────┘
                                   │
                    ┌──────────────────────────────┐
                    │ Assess adequate use of treatment options│
                    │ Provide new instructions and counselling │
                    │ Re-trial                                 │
                    │ Consider alternative or combination therapy│
                    └──────────────────────────────┘
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                    │ Inadequate treatment outcome   │
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                    │ Consider penile prosthesis implantation│
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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 [60]. 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) [60, 91]. When clinically indicated [33], testosterone supplementation (TS) (intramuscular, oral, or transdermal) is effective, but should only be used after other endocrinological causes for testicular failure have been excluded [31, 57, 92]. Before initiating TS, digital rectal examination, serum PSA test, haematocrit, liver function tests and lipid profile should be performed [31, 57]. Patients who are given TS should be monitored for clinical response, elevation of haematocrit and development of hepatic or prostatic disorders [31, 57]. TS is controversial in men with a history of PCa (LE: 4) [93]. 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).

TS is contraindicated in patients with unstable cardiac disease. 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 [94-99]. 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 patients with heart disease to improve survival [56]. However, a recent comprehensive SR and meta-analysis of all placebo-controlled randomised clinical trials (RCTs) on the effect of TS on cardiovascular-related problems did not support a causal role between TS and adverse cardiovascular events [100].

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 [101]. 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 [101].

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. Psychosexual therapy requires ongoing follow-up and has had variable results [102].

3.1.4.2   First-line therapy
3.1.4.2.1   Oral pharmacotherapy

PDE5 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 a penile erection [103]. Four potent selective PDE5Is have been approved by the European Medicines Agency (EMA) for the treatment of ED [104]. 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 [105]. 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. Sildenafil is effective from 30-60 min after administration. Its efficacy is reduced after a heavy, fatty meal due to delayed absorption. Efficacy may be maintained for up to 12 hours [106]. 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 [107, 108]. 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 [105]. 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. (GR: A, 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 licenced for treatment of ED in February 2003 and is effective from 30 min after administration, with peak efficacy after about 2 h. Efficacy is maintained for up to 36 hours [109] 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. 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 12 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 [109]. Tadalafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies. The efficacy of tadalafil in almost every subgroup of patients with ED, thus including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A [110]. Daily tadalafil has also been licensed for the treatment of LUTS secondary to BPH. Therefore, it is useful in comorbid patients with ED and LUTS.

Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 min after administration [110]. Its effect is reduced by a heavy, fatty meal (> 57% fat). Five, 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 [111]. Pharmacokinetic data of vardenafil are presented in Table 5. Adverse events (Table 6) are generally mild in nature and self-limited by continuous use [111]. After 12 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 [111, 112]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. Efficacy has been confirmed in post-marketing studies [111, 112]. The efficacy of vardenafil in almost every subgroup of patients with ED, thus including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. The overall level of evidence and grade of recommendation is Level 1 Grade A. More recently, an ODT of vardenafil has been released [112]. Orodispersable 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 bioavailability compared to film-coated tablets [113]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [113, 114].

Avanafil

Avanafil is a highly-selective PDE5I that became commercially available in 2013 [115]. 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 [116]. 50, 100, and 200 mg doses have been approved for on-demand treatment of ED [115]. 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 [115, 117, 118]. 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 [115, 117]. Data from sexual attempts made within 15 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 [117]. Pharmacokinetic data of avanafil are presented in Table 5 [115, 117]. Adverse events are generally mild in nature (Table 6) [115, 117]. 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 [114, 115]. 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. The overall level of evidence and grade of recommendation is Level 1 Grade A.

Choice or preference between the different PDE5 inhibitors

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, 3-4 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.

Continuous use of PDE5 inhibitors

Animal studies have shown that chronic use of PDE5Is significantly improves or prevents the intracavernous structure alterations due to age, diabetes, or surgical damage [119-123]. 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 [124]. In 2007, tadalafil 2.5 and 5 mg have been 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 reassessed periodically [124, 125]. 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 PDE5 inhibitors 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	1685 µg.h/L	8066 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 halftime; AUC: area under curve or serum concentration time curve.

Table 6: Common adverse events of the four PDE5 inhibitors 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 PDE5 inhibitors

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-ischaemia 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 6 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.

Nitrates are contraindicated with PDE5 inhibitors

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 ("poppers" 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 h if sildenafil (and probably also vardenafil) is used (half-life, 4 h), or at least 48 h if tadalafil is used (half-life, 17.5 h), and for no less than 12 h if avanafil is used (half-life, 6-17 h) [126].

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. 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.

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 4 hours following treatment with an α-blocker. A starting dose of 25 mg is recommended [107].
- 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 [110-112].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [109, 127].
- 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 CYP34A pathway will inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (among them, 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 PDE5 inhibitors

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 [128]. 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.

Lack of adequate sexual stimulation: 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 [106, 108, 113, 114, 129-131]. 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 [108, 113, 114, 129-131], most patients require a longer delay between taking the medication [111, 114, 132, 133]. Absorption of sildenafil can be delayed by a meal, and absorption of vardenafil can be delayed by a fatty meal [134]. Absorption of tadalafil is less affected provided there is enough delay between oral ingestion and an attempt at sexual intercourse [129]. 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 [114-116].

It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about 4 hours, suggesting that the normal window of efficacy is 6-8 h following drug ingestion, although responses following this time period are well recognised. The half-life of avanafil is 6-17 h. Tadalafil has a longer half-life of ~17.5 h, 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. 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 [135-137].

Clinical strategies in patients correctly using a PDE5 inhibitor
There is controversial evidence suggesting that, in patients with testosterone deficiency, TS might improve response to a PDE5I [57, 138-140]. 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 [141]. 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 PDEI (such as sildenafil), without any significant increase in terms of side-effects [142]. 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).

3.1.4.2.2   Vacuum erection devices
VEDs 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% [143, 144]. Most men who discontinue use of VEDs do so within 3 months. Long-term use of VEDs decreases to 50-64% after 2 years [145]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness, which occur in < 30% of patients [144]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes after intercourse.. VEDs are contraindicated in patients with bleeding disorders or on anticoagulant therapy. VEDs 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 [143, 144].

3.1.4.2.3   Shockwave therapy
Recently, the use of low-intensity extracorporeal shock wave therapy (LI-SWT) was proposed as a novel treatment for ED [146]. In the first randomised, double-blind, sham-controlled study, it was demonstrated that LI-SWT had a positive short-term clinical and physiological effect on the erectile function of men who respond to PDE5Is [147]. Moreover, there are preliminary data showing improvement in penile haemodynamics and endothelial function, as well as IIEF erectile function domain score in severe ED patients who are poor responders to PDE5Is [148, 149]. Current data are still limited and 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%) [150, 151]. Intracavernous administration of vasoactive drugs was the first medical treatment for ED introduced more than 20 years ago [152, 153].

3.1.4.3.1   Intracavernous injections
3.1.4.3.1.1 Alprostadil
Alprostadil (CaverjectTM, Edex/ViridalTM) was the first and only drug approved for intracavernous treatment of ED [152, 153]. 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 5-15 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 after 94% of the injections and satisfaction rates of 87-93.5% in patients and 86-90.3% in partners [152, 153]. 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%) [152-154]. Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia [152, 153, 155]. 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 [152, 153, 156, 157], with most drop-outs occurring within the first 2-3 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 [158].

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 [159, 160]. 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 [161, 162]. 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).
- VIP (25 μg) + phentolamine mesylate (1-2 mg) (InvicorpTM, 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 [163].

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 [164]. 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 [165]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, only the higher doses (500 and 1000 μg) have been used with low consistency response rates [165-167]. The application of a constriction ring at the root of the penis (ACTIS™) may improve efficacy [166, 167].

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 [151]. 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 [168]. 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 [169]. 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. The two currently available classes

of penile implants include inflatable (2- and 3-piece) and malleable devices [38, 89, 170, 171]. 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 [38, 89, 170, 171].

There are two main surgical approaches for penile prosthesis implantation: penoscrotal and infrapubic [170-173]. 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 [38, 89, 170, 174-180]. 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 [38, 89, 181-183].

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/CXRTM and Coloplast Alpha ITM) resulted in mechanical failure rates of < 5% after 5 years of follow-up [89, 184, 185]. 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. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [89, 186-189]. 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 [15, 89, 170, 190-192]. 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 [190, 192, 193]. The majority of revisions are secondary to mechanical failure and combined erosion or infection. Ninety three percent of cases are successfully revised, providing functioning penile prosthesis.

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 ED treatment.	1a	A
Start pro-erectile treatments at the earliest opportunity after RP.	1b	A
Treat a curable cause of ED first, when found.	1b	B
Use 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 VED 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

ED = erectile dysfunction; RP = radical prostatectomy; VED = vacuum erection devices;
PDE5I = phosphodiesterase type 5 [inhibitors].

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 [194]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the USA National Health and Social Life Survey (NHSLS) study [195]. 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 [196]. According to the four PE subtypes proposed by Waldinger *et al.* [197], the prevalence rates were 2.3% (lifelong PE), 3.9% (acquired PE), 8.5% (natural variable PE) and 5.1% (premature-like ejaculatory dysfunction) [198]. 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 [199].

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 [200]. 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 [201]. 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 [195, 196], unlike ED, which increases with age. PE is not affected by marital or income status [195]. However, PE is more common in black men, Hispanic men and men from Islamic backgrounds [202, 203] and may be higher in men with a lower educational level [195, 201]. Other risk factors may include a genetic predisposition [204], poor overall health status and obesity [195], prostate inflammation [205, 206], thyroid hormone disorders [207], emotional problems and stress [195, 208], and traumatic sexual experiences [195, 201]. In the only published study on risk modification/prevention strategies [209], 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 [210].

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 [211, 212]. However, the negative impact of PE extends beyond sexual dysfunction. PE can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [211, 213]. Sex drive and overall interest in sex does not appear to be affected by PE [214]. However, the partner's satisfaction with the sexual relationship decreases with increasing severity of the man's condition [215]. 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 [201], with men more likely to seek treatment for ED than for PE [201]. In the Premature Ejaculation Prevalence and Attitudes survey, only 9% of men with self-reported PE consulted a doctor [196]. 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 [216, 217]. 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*' [218]. This DSM definition has been recently updated in the DSM V edition [219].
- In the World Health Organization's International Classification of Diseases-10 (ICD-10), PE is defined as '*the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity*' [220].

The Second International Consultation on Sexual and Erectile Dysfunction defined PE as:
'*ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother or distress, and over which the sufferer has little or no voluntary control*' [200].

The International Society for Sexual Medicine (ISSM) has adopted a completely new definition of PE which is the first evidence-based definition [221]:
PE (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 3 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.

All four definitions have taken into account the time to ejaculation, the inability to control or delay ejaculation, and negative consequences (bother/distress) from PE. However, the major point of debate is quantifying the time to ejaculation, which is usually described by IELT [219].

Recently, two more PE syndromes have been proposed [222]:
- '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 [223].

3.2.3 Diagnostic evaluation

Diagnosis of PE is based on the patient's medical and sexual history [224, 225]. 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 [226]. 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 [227]. There are several overlapping definitions of PE, with four shared factors (Table 7), resulting in a multidimensional diagnosis [228].

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 [229, 230]. IELT 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 [231]. 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 [232]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [233]. 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, 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 [234].

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 [228]. 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 [235, 236]. 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 [237]. 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 [238]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [239]. Other questionnaires used to characterise PE and determine treatment effects include the PEP [230], Index of Premature Ejaculation (IPE) (61) and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [240]. 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 [224].

3.2.3.4 Recommendations for the diagnostic evaluation of PE

Recommendations	LE	GR
Perform the diagnosis and classification of PE based on medical and sexual history, which should include assessment of 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 (PROs) 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 ED.	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

PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; ED = erectile dysfunction.

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 to treat first, if present, ED especially 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 reuptake 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 [241] and its modification, the 'squeeze' technique, proposed by Masters and Johnson:
- 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 [242].

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. 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.

Overall, short-term success rates of 50-60% have been reported [243, 244]. However, there is no controlled research to support the efficacy of behavioural techniques, while a double-blind, randomised, crossover study showed that pharmacological treatment (chlomipramine, sertraline, paroxetine and sildenafil) resulted in greater IELT prolongation than behavioural therapy [245]. Furthermore, clinical experience suggests that improvements achieved with these techniques are generally not maintained long-term [246, 247]. 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 [248]. 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) [249]. Dapoxetine has been investigated in 6,081 subjects to date [250]. 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 [251, 252]. In RCTs, dapoxetine, 30 mg or 60 mg 1-2 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 [252]. 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 [232]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [253].

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 selective serotonin re-uptake inhibitors (SSRIs) administered alone. Generally, when dapoxetine is co-administered with a PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [254]. 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 [255].

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 reuptake 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 autoreceptor activation and compensation reported using chronic SSRIs, or these effects occur, but they simply cannot prevent the action of short-acting SSRIs [256].

3.2.4.2.2   Off-label use of antidepressants: SSRIs and clomipramine
Ejaculation is commanded by a spinal ejaculation generator [257, 258] 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 [256].

SSRIs 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 [256]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT1A and 5-HT1B receptors [260]. Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1973 as an effective PE treatment [261]. SSRIs have revolutionised treatment of PE, but they have also changed our understanding of PE since the first publication on paroxetine in 1970 [262]. 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.

A systematic review and meta-analysis 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 [263]. 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 [264, 265].

Ejaculation delay may start a few days after drug intake, but it is more evident after one to two weeks since receptor desensitisation 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 [261]. 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 [223, 251]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of a theoretical risk of suicidal thoughts or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents with PE aged 18 years or less, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal thoughts. 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 [232].

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 [266]. However, on-demand treatment may be combined with an initial trial of daily treatment or concomitant low-dose daily treatment reducing adverse effects [267, 268]. 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 [269]. Several trials [270, 271] 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.

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 [272]. In another randomised, double-blind, placebo-controlled trial, lidocaine-prilocaine cream significantly increased the stopwatch-measured IELT from 1.49 to 8.45 minutes while no difference was recorded in the placebo group (1.67 to 1.95 minutes) [273]. 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 [272]. 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 contra-indicated 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 5 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 3 months of double-blind treatment; a 3.3-fold delay in ejaculation compared with placebo (p < 0.001) [274].

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 [275]. 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 [276].

A large, randomised, double-blind, placebo-controlled, multicentre 12-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by orally disintegrating tablet (ODT) in the treatment of PE [277]. 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 12-week study period was acceptable.

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 [278]. 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 sildenafil combined with an SSRI is superior to SSRI monotherapy:
•   Sildenafil combined with paroxetine improved IELT significantly and satisfaction vs. paroxetine alone [279].
•   Sildenafil combined with sertraline improved IELT and satisfaction significantly vs. sertraline alone [280].
•   Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [281].
•   Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction vs. behavioural therapy alone [282].

There are very limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [283, 284]. The role of PDE5Is in PE patients without ED is not established, with only minimal double-blind placebo controlled data available.

3.2.4.3   Summary of evidence on the epidemiology/aetiology/pathophysiology of ED

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.	1a	A
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with SSRIs.	1b	A
Use tramadol on demand as a weak alternative to SSRI's.	2a	B
Do not use PDE5Is in patients with PE without ED.	3	C
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired premature ejaculation.	3	C

SSRI = selective serotonin reuptake inhibitor.

Figure 4: Management of Premature Ejaculation*

> ## Clinical diagnosis of premature ejaculation based on patient +/- partner history
> - Time to ejaculation (IELT)
> - Perceived degree of ejaculatory control
> - Degree of bother/stress
> - Onset and duration of PE
> - Psychosocial/relationship issues
> - Medical history
> - Physical examination

> ## Treatment of premature ejaculation
> Patient counselling/education
> Discussion of treatment options
> If PE is secondary to ED, treat ED first or concomitantly

> - Pharmacotherapy (recommended as first-line treatment option in lifelong PE)
>   - o Dapoxetine for on-demand use (the only approved drug for PE)
>   - o Off-label treatments include chronic daily use of antidepressants (SSRIs or clomipramine) and topical anaesthetics or oral tramadol on demand
> - Behavioural therapy, includes stop-start technique, squeeze and sensate focus
> - Combination treatment

* Adapted from Lue *et al.* 2004 [285].
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% [286] while there are reports from studies with poor quality which claim that it is more common with prevalence rates of 4-10% in the absence of hypospadias [287].

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 [288].

3.3.1.3   Disease management

The treatment of this disorder is surgical correction deferred until after puberty. 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 [289]. 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 [290-292].

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 (PD) disease are limited. Prevalence rates of 0.4-9% have been published, with a higher prevalence in patients with erectile dysfunction (ED) and diabetes [293-300]. The typical age of a patient with PD is 55-60 years.

3.3.2.1.2   Aetiology

The aetiology of Peyronie's disease 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 [301]. A prolonged inflammatory response will result in the remodelling of connective tissue into a fibrotic plaque [301-303]. 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 [296, 300, 304, 305]. Dupuytren's contracture is more common in patients with Peyronie's disease affecting 9-39% of patients [297, 306-308] while 4% of patients with Dupuytren's contracture reported Peyronie's disease [307].

3.3.2.1.4   Pathophysiology

Two phases of the disease can be distinguished [309]. 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 [304, 310, 311]. Pain is present in 35-45% of patients during the early stages of the disease [312]. Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset of the disease [310, 311].

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 [313].

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 (PDQ) has been designed to collect data, and it has been validated for use in clinical practice [314].

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 [310].

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 [311]. 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 [315]. Measurement of penile length during erection is important because it may have impact on the subsequent treatment decisions [316].

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 [317]. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in Peyronie's disease patients [33]. ED is common in patients with Peyronie's disease (> 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 [19, 30]. The presence of ED and psychological factors may impact on the treatment strategy [318].

Ultrasound (US) measurement of the plaque's size is inaccurate and it is not recommended in everyday clinical practice [319]. Doppler US may be required for the assessment of vascular parameters [318].

3.3.2.2.1   Summary of evidence and recommendations for the diagnosis of Peyronie's disease

Summary of evidence	LE
US measurement of the plaque's size is inaccurate and operator dependent.	3
Doppler US is required to ascertain vascular parameters associated with erectile dysfunction.	2a

Recommendations	LE	GR
In the medical and sexual history in 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 PDQ in everyday clinical practice.	2a	B
Do not use US measurement of plaque size in everyday clinical practice.	3	C
Use Doppler US only in the case of diagnostic evaluation of ED, to ascertain vascular parameters associated with erectile dysfunction.	2a	B

PDQ = Peyronie's disease-specific questionnaire; US = ultrasound.

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 [311, 320]. 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 injection in patients with densely fibrotic or calcified plaques have been also suggested [309, 321]. Clostridium collagenase is the only drug approved for the treatment of Peyronie's disease by the FDA. No single drug has been approved by the EMA for the treatment of Peyronie's disease at this time. The results of the studies on conservative treatment for Peyronie's disease 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 [321]. 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 (PDE5i)
Intralesional treatments
Steroids
Verapamil
Clostridium collagenase
Interferon
Topical treatments
Verapamil
Iontophoresis
Extracorporeal shock wave treatment (ESWT)
Traction devices
Vacuum 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 [322]. A double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size [323]. Moreover, there is conflicting evidence as to long-term cardiovascular effects of vitamin E usage at large doses, which urologists use for penile deformity treatment [324].

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 [325]. Preliminary studies reported an improvement in penile curvature, penile plaque size, and penile pain during erection [326]. In a prospective double-blinded controlled study in 41 patients with Peyronie's disease, Potaba (12 g/day for 12 months) improved penile pain significantly, but not penile curvature or penile plaque size [327]. In another similar study in 103 patients with Peyronie's disease, Potaba decreased penile plaque size significantly, but had no effect on penile curvature or penile pain [328]. 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 [329].

Tamoxifen

Tamoxifen is a non-steroidal oestrogen receptor antagonist modulating transforming growth factorβ1 (TGFβ1) 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 [330]. However, a placebo-controlled, randomised study (in only 25 patients, at a late stage of the disease with a mean duration of 20 months) using the same treatment protocol, failed to show any significant improvement in pain, curvature, or plaque size in patients with Peyronie's disease [331].

Colchicine

Colchicine has been introduced into the treatment of Peyronie's disease on the basis of its anti-inflammatory effect [332]. 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% out of 24 men [333]. In another study in 60 men (colchicine 0.5-1 mg daily for 3-5 months with escalation to 2 mg twice daily), penile pain resolved in 95% and penile curvature improved in 30% [332]. Similar results have been reported in another uncontrolled retrospective study in 118 patients [334]. Reported treatment-related adverse events with colchicine are gastrointestinal effects (nausea, vomiting, diarrhoea) that can be improved with dose escalation [332].

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 Peyronie's disease resulted in significant improvement in plaque size and curvature, but not in pain compared to ibuprofen 400 mg/day for 6 months [335].

Acetyl esters of carnitine

Acetyl-L-carnitine and propionyl-L-carnitine are proposed to inhibit acetyl coenzyme-A and produce an antiproliferative 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 Peyronie's disease, patients were randomised to acetyl-L-carnitine (1 g twice daily) compared to tamoxifen (20 mg twice daily). After 3 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) [336]. 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 3 months) significantly reduced penile curvature, plaque size, and disease progression compared to intralesional verapamil combined with tamoxifen (40 mg/day) for three months [337].

Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase inhibitor which down-regulates TGFβ1 and increases fibrinolytic activity [338]. Moreover, an increase of NO levels may be effective in preventing progression of Peyronie's disease or reversing fibrosis [339]. 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 [339]. In another study in 62 patients with Peyronie's disease, pentoxifylline treatment for six months appeared to stabilise or reduce calcium content in penile plaques [340].

Phosphodiesterase type 5 inhibitors

The rationale for the use of PDE5Is in Peyronie's disease 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 Peyronie's disease-like plaque [341]. 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 [342]. Therefore, no recommendation can be given for PDE5Is in patients with Peyronie's disease.

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 [343]. In small, non-randomised, studies, a decrease in penile plaque size and pain resolution was reported [344, 345]. 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 [346]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [344].

Verapamil
The rationale for intralesional use of verapamil (a calcium channel antagonist) in patients with Peyronie's disease is based on in-vitro research [347, 348]. A number of studies have reported that intralesional verapamil injection may induce a significant reduction in penile curvature and plaque volume [349-353]. 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 [352]. Side-effects are uncommon (4%). Minor side-effects include nausea, light-headedness, penile pain, and ecchymosis [352]. 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 [354]. Younger age and larger baseline penile curvature were found to be predictive of favourable curvature outcomes in a case-series study [355].

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 Peyronie's disease plaque [356-358]. Clostridium collagenase is now approved by the 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 551 treated men with CCH 60.8% were global responders compared with 29.5% of 281 who received placebo. The most commonly reported side-effects were penile pain, penile swelling, and ecchymosis at the site of injection [359]. Of note, CCH is available in the US only through a restricted programme under a Risk Evaluation and Mitigation Strategy (REMS) because of the risks of serious adverse reactions, including penile fracture and other serious penile injury. CCH should be administered by a healthcare professional who is experienced in the treatment of male urological diseases. The REMS requires participating healthcare professionals to be certified within the programme by enrolling and completing training in the administration of CCH treatment for Peyronie's disease. The REMS also requires healthcare facilities to be certified within the program and ensure that CCH is dispensed only for use by certified healthcare professionals [360].

Interferon
Interferon α-2b has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improved the wound healing process from Peyronie's disease plaques in-vitro [361]. Intralesional injections (5 x 10^6 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 [362, 363]. 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.

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 [364]. 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 [365, 366].

Extracorporeal shock wave treatment

The mechanism of action involved in shock wave treatment (ESWT) for Peyronie's disease is still unclear, but there are two hypotheses. In the first hypothesis, shock wave therapy works by directly damaging and remodelling the penile plaque. In the second hypothesis, shock wave 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 [367]. Most uncontrolled studies failed to show significant improvements in patients with Peyronie's disease [368-370]. In a prospective, randomised, double-blind, placebo-controlled study, four weekly treatment sessions of ESWT, with each session consisting of 2,000 focused shock waves, resulted in significant improvement only for penile pain [371].

Traction devices

The application of continuous traction in Dupuytren's contracture increases the activity of degradative enzymes [372]. This initially leads to a loss of tensile strength and ultimately to solubilisation. It is followed by an increase in newly synthesised collagen [372]. 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/day for six months [89]. Reduced penile curvature of 10-40° was found in all men with an average reduction of 33% (range: 51-34º). 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 two to eight hours daily for an extended period, but has been shown to be tolerated by highly motivated patients [307]. 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 [373].

Vacuum devices

The application of vacuum devices follows the same principles as traction devices with the drawback of being non-continuous precluding remodelling of the plaque. Their efficacy has been assessed in an uncontrolled study (31 patients completed the study) [374]. Half of the patients were satisfied with the outcome and the remaining had their curvature corrected surgically.

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 Peyronie's disease 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 clostridium collagenase 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 shock-wave 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 shock-wave treatment to improve penile curvature and 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 Peyronie's disease 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 [73]. Patients must have a stable disease for at least three months, although a six to twelve month period has also been suggested [375].

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 [309]. Two major types of repair may be considered for both congenital penile curvature and Peyronie's disease: penile shortening and penile lengthening procedures [376].

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 [376]. However, recent data suggest that circumcision is not always necessary e.g. in cases where the foreskin is normal pre-operatively [377]. Finally, in patients with Peyronie's disease and ED not responding to medical treatments, surgical correction of the curvature with concomitant penile prosthesis implantation should be considered [378].

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 [309]. Patient expectations from surgery must also be included in the pre-operative assessment. There are no standardised questionnaires

for the evaluation of surgical outcomes [73]. 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 [309, 379].

3.3.2.3.2.1 Penile shortening procedures

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite a non-elastic corporal segment to treat congenital penile curvature [380]. Fourteen years later, this technique became a successful treatment option, also for Peyronie's disease [381]. 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 [376]. The overall short- and long-term results of the Nesbit operation are excellent. Complete penile straightening is achieved in more than 80% of patients [382]. Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of post-operative ED is minimal [376, 383]. Penile shortening is the most commonly reported outcome of the Nesbit procedure [383]. 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 [381, 384]. Patients often perceive the loss of length as greater than it actually is [382, 383]. 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) [385].

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 [386-391]. Another modification has been described as the '16 dot' technique with minimal tension under local anaesthesia [392]. The use of non-absorbable sutures reduced recurrence of the curvature. Results and satisfaction rates are similar to the Nesbit procedure [376]. 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 [393].

Devine and Horton introduced dermal grafting in 1974 [394]. Since then, a variety of grafting materials and techniques have been reported (Table 10) [395-409]. 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 [410].

Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. Saphenous vein is the most common vein draft used, followed by dorsal penile vein [376]. In the first case, a secondary incision for graft harvesting is avoided. Postoperative curvature (20%), penile shortening (17%) and graft herniation (5%) have been reported after vein graft surgery [400, 405, 408]. Tunica vaginalis is relatively avascular, easy to harvest and has little tendency to contract due to its low metabolic requirements [398].

Dermal grafts are commonly associated with contracture resulting in recurrent penile curvature (35%), progressive shortening (40%), and a 17% re-operation rate at 10 years [411]. Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multi-directional elasticity/expansion by 30% [409]. 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 [409, 411].

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 [406].

More recently the use of buccal mucosa grafts (BMG) has been advocated. BMG 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 [397].

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 [412]. 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 [378]. 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 [376]. 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 [399].

The use of a penile extender device on an 8- to 12-hour daily regimen has been advocated as an effective and safe treatment for loss of penile length in patients operated on for Peyronie's disease [413].

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

3.3.2.3.2.3 Penile prosthesis
Penile prosthesis implantation is typically reserved for the treatment of Peyronie's disease 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 [408].

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 [415, 416]. 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 [415]. 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 [414, 417, 418].

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 [416].

Table 10: Results of surgical treatments for Peyronie's disease (data from different, non-comparable studies) [381, 383-409, 411, 412]

| | Tunical lengthening procedures | | Tunical shortening 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 penile prosthesis, 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
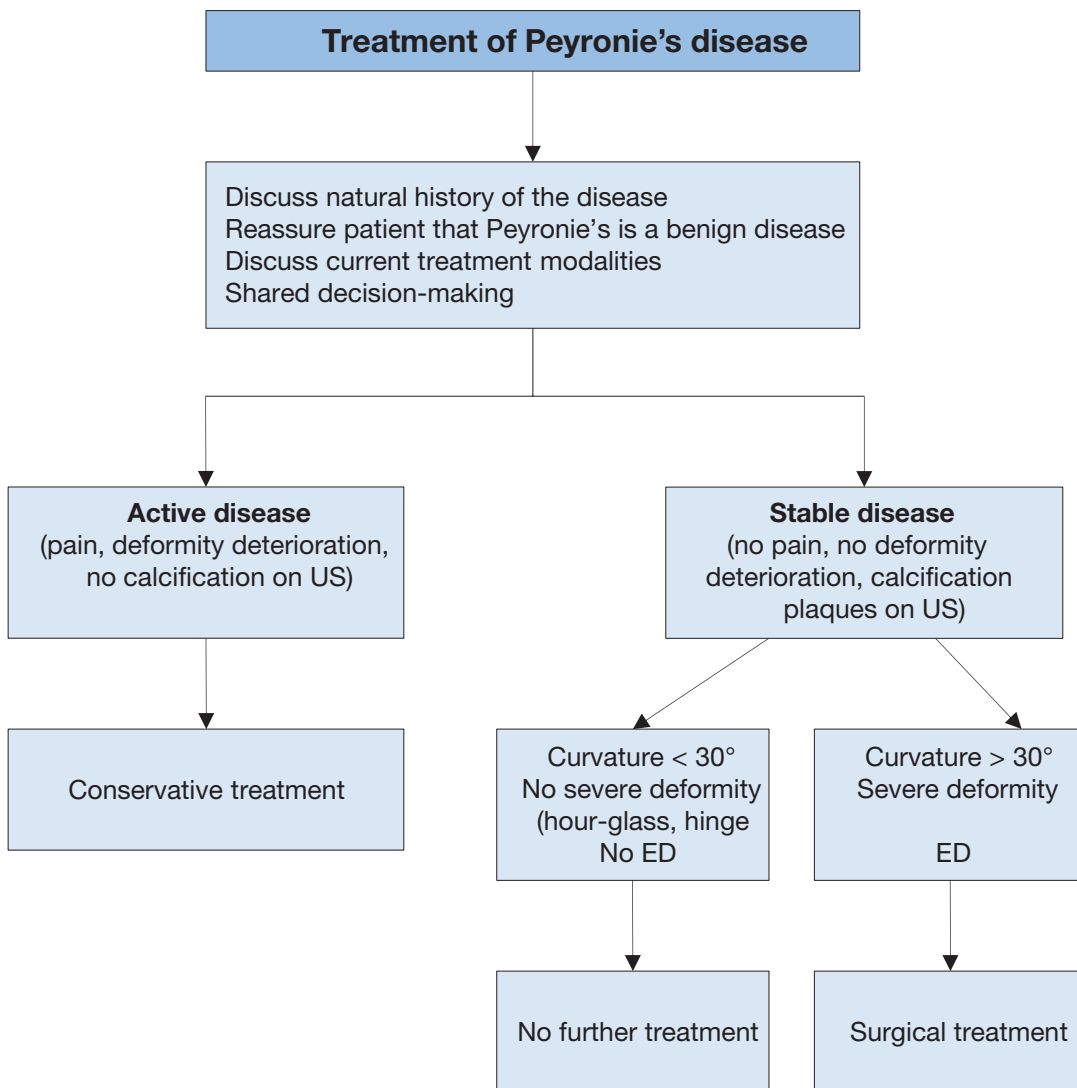
ED = erectile dysfunction; US = Ultrasound.

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 Peyronie's disease. The risk of erectile
dysfunction seems to be greater for penile lengthening procedures [309, 376]. Recurrent curvature implies either failure to wait until the disease has stabilised, a reactivation 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 [94]. Accordingly, it is recommended that only non-absorbable sutures or slowly reabsorbed 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 [383]. 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 for a dorsal deformity [376].

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 3 months (without pain or deformity deterioration), which is usually the case after 12 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 [419, 420]. 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 modifications in the corporal metabolic environment, progressively leading to hypoxia, hypercapnia, glucopenia and acidosis.

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 [421, 422]. The duration of priapism represents the most significant predictor for the development of ED. In this context, interventions beyond 48-72 hours since the onset may help to relieve the erection and pain, but have little benefit in preventing long-term ED.

Histologically, by twelve hours, corporal specimens show interstitial oedema, progressing to destruction of 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 pathophysiology (Table 11), no specific cause can be identified in the majority of cases [420, 423]. However, ischaemic priapism can be associated with sickle cell disease, haematological dyscrasias, neoplastic syndromes, and with the use of several different medications. Ischaemic priapism may occur (0.4-35%) after intracavernous injections of erectogenic agents [150, 420, 421, 424, 425]. The risk is highest with papaverine-based combinations, while the risk of priapism is < 1% following prostaglandin E1 injection [425].

Since their introduction on the market, a few cases of priapism have been described in men who have taken PDE5Is [420]. Most of these men however, had other risk factors for priapism, and it is unclear whether PDE5Is alone can cause ischaemic priapism [420]. 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 [426], with a lifetime probability of developing ischaemic priapism of 29-42% in men with sickle cell disease [420, 426-428] (LE: 4). Mechanisms of sickle cell disease associated priapism may involve dysfunctional nitric oxide synthase and Rho-associated protein kinase (ROCK) signaling, and increased oxidative stress associated with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase mediated signaling [429].

Priapism resulting from metastatic or regional infiltration is rare and usually reflects an infiltrative process [430]. 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 and be offered supportive care 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 thrombosis of the penis, is a very rare condition. It is a subtype of priapism limited to a single crura. Its aetiology is unknown, but bicycle riding, trauma, drug usage, sexual intercourse, haematological diseases and α-blockers have been associated with partial priapism [431]. There may be a congenital web in the corpora which poses a risk factor [432].

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
o	Vasoactive erectile agents (i.e. papaverine, phentolamine, prostaglandin E1/alprostadil, combination of intracavernous therapies)
o	Alpha-adrenergic receptor antagonists (i.e. prazosin, terazosin, doxazosin, tamsulosin)
o	Antianxiety agents (hydroxyzine)
o	Anticoagulants (heparin, warfarin)
o	Antidepressants and antipsychotics (i.e. trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thiorizadine, phenothiazines)
o	Antihypertensives (i.e. hydralazine, guanethidine, propranolol)
o	Hormones (i.e. gonadotropin-releasing hormone, testosterone)
o	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

PDE5Is = phosphodiesterase type 5 inhibitors.

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 [420]. 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
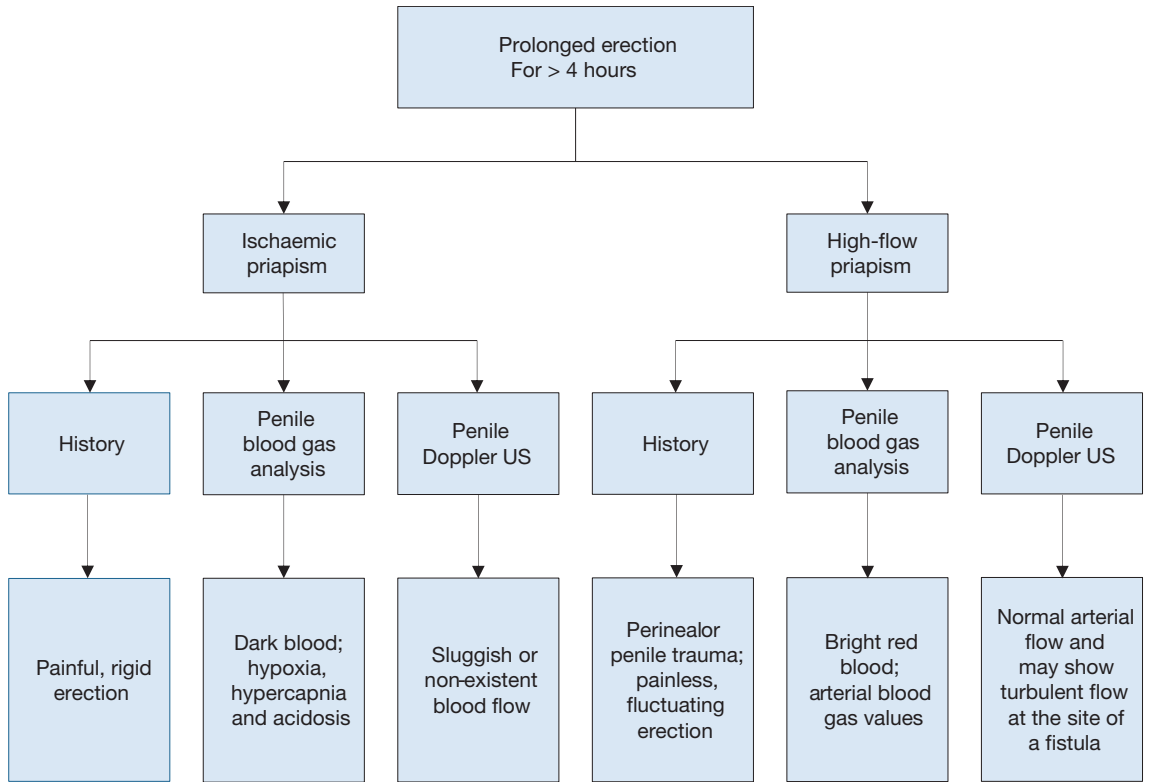
3.4.1.3.1 History
A comprehensive history taking is the mainstay in priapism diagnosis [420, 433]. The medical history must include a history of sickle cell disease or any other haematological abnormality [8, 434] and a history of pelvic, genital or perineal trauma. The sexual history must include complete details of the duration of 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 type of priapism (Table 13). Ischaemic priapism is 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.* [420])

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 [420, 433].

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 ultrasound (US) of the penis and perineum is recommended and can differentiate ischaemic from arterial priapism as an alternative or adjunct to blood gas analysis [435-437] (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 [420, 437, 438]. 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 [439]. 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.* [420])

	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.* [420]

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

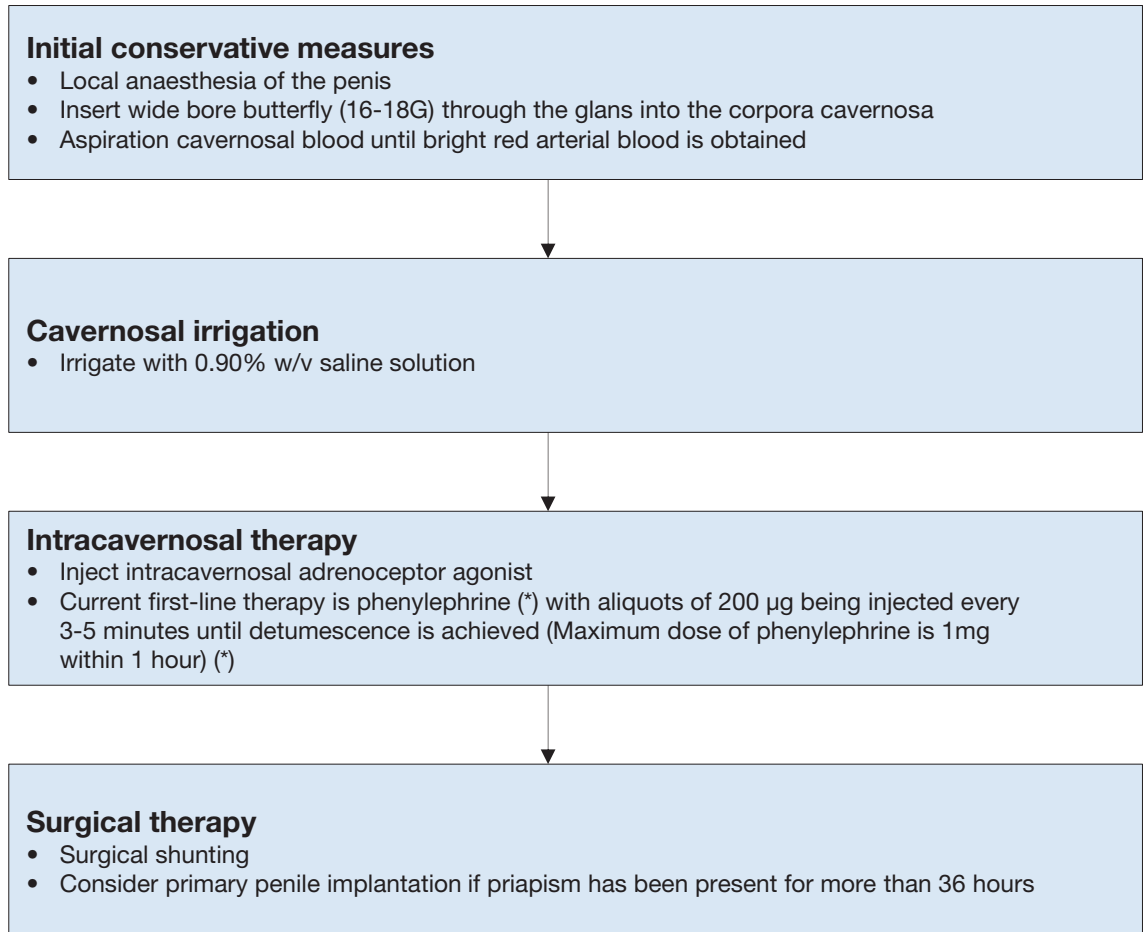| Recommendations	GR
Take a comprehensive history for diagnosis which can help to determine the underlying type of priapism.	B
Include physical examination of the genitalia, the perineum and the abdomen in the diagnostic evaluation which may help to determine the underlying type of priapism.	B
For laboratory testing, include complete blood count, white blood count with blood cell differential, platelet count and coagulation profile. Direct further laboratory testing by the history and 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.

Initial conservative measures
- Local anaesthesia of the penis
- Insert wide bore butterfly (16-18G) through the glans into the corpora cavernosa
- Aspiration cavernosal blood until bright red arterial blood is obtained

↓

Cavernosal irrigation
- Irrigate with 0.90% w/v saline solution

↓

Intracavernosal therapy
- Inject intracavernosal adrenoceptor agonist
- Current first-line therapy is phenylephrine (*) with aliquots of 200 µg being injected every 3-5 minutes until detumescence is achieved (Maximum dose of phenylephrine is 1mg within 1 hour) (*)

↓

Surgical therapy
- Surgical shunting
- Consider primary penile implantation if priapism has been present for more than 36 hours

(*) 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 > 4 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 [420]. 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 [440].

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 0.90% w/v saline solution
The first intervention for an episode of priapism lasting > 4 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 16G or 18G 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 [427] (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 [3, 420, 441] (LE: 4). Pharmacological agents include sympathomimetic drugs or alpha-adrenergic agonists. Options for intracavernous sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80%. [420, 441-449] (LE: 2b). The use of intracavernous adrenalin injection alone has also been sporadically reported [450].

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 [442, 446, 447] (LE: 4).

Phenylephrine is diluted in normal saline to a concentration of 100-500 µg/mL. Usually 200 µg 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 [420, 441-443, 446, 447] and it is recommended that blood pressure and pulse are monitored every 15 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 [34]. 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
Etilefrine 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 [443] (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 [451, 452] (LE: 3). Methylene blue, 50-100 mg [451], should be injected intracavernously and left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes [452]. 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 [450]), has been used in patients with ischaemic priapism due to an intracavernous injection of vasoactive agents. 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 beta-2-agonist with minor β-1 effects and some alpha-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 [453-455] (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 [455].

Table 15: Medical treatment of ischaemic priapism

Drug	Dosage/Instructions for use
Phenylephrine	• Intracavernous injection of 200 μg every 3-5 minutes. • Maximum dosage is 1 mg within 1 hour. • The lower doses are recommended in children and patients with severe cardiovascular disease.
Etilephrine	• Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL normal saline.
Methylene blue	• Intracavernous injection of 50-100 mg, left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes.
Adrenaline	• Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period.
Terbutaline	• 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 coordinated with a haematologist [456-458] (LE: 4).

However, as with other haematological disorders, other therapeutic practices may also need to be implemented [456, 458, 459]. 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 [428, 457].

Exchange blood transfusion has also been proposed, with the aim of increasing the tissue delivery of oxygen. The transfused blood should be HbS negative, Rh and Kell antigen matched [460]. 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 [461]. 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 [420, 441, 462].

In general, the type of shunt procedure chosen is according to the surgeon's preference and procedure familiarity (LE: 4). It is conventional for distal shunt procedures to be tried before proximal shunting is considered (LE: 4). Cavernous biopsy has been used to identify muscle necrosis (which, if present, would suggest that shunting is likely to fail) although this has mainly a medico-legal role.

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) [420, 441].

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 [463, 464]. Priapism for more than 36 hours appears to irreversibly impair erectile tissue both structurally and functionally [463]. In general, shunt procedures undertaken after this time period may only serve to limit pain without any benefit for erectile function (LE: 4) [465, 466].

Four categories of shunt procedures have been reported [3, 420, 462]. 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 body [3, 420, 426, 467, 468] (LE: 3). Postoperative sequelae are uncommon [469]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [464].

Ebbehoj's technique: this technique involves the execution of 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 [3, 420, 467, 470, 471] (LE: 3).

T-Shunt: this technique involves performing a bilateral procedure using a size 10 blade scalpel placed vertically through the glans until fully within the corpus cavernosum. The blade is then rotated 90° away from the urethra and pulled out [3, 420, 467, 472] (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 [472].

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 [3, 420, 467, 473, 474] (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 [3, 420, 467, 475, 476] (LE: 3). Reported complications included wound infection, penile skin necrosis and a urethrocutaneous fistula [476].

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 cavenosum and the corpus spongiosum. The most frequent complications include an unwanted urethra-cavernous fistula and urethral stricture or the development of cavernositis [3, 420, 462, 477]. 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 [3, 420, 478-480] (LE: 3).

Immediate surgical prosthesis implantation
Intractable, 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 [481-484] (LE: 3).

The immediate insertion of a 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 [481, 483], along with a mild rate of revision surgery [481]. Early surgery also offers the opportunity to maintain penile size, and prevent penile curvature due to cavernosal fibrosis .

Currently, there are no clear indications for immediately implanting a penile prosthesis in a man with acute ischaemic priapism [441]. Relative indications include [420] (LE: 4):
- ischaemia that has been presented for more than 36 hours [484];
- 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);
- MRI or corporal biopsy evidence of corporal smooth muscle necrosis [420, 481] (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, [462, 481, 485, 486]. Erectile dysfunction is also often observed [420, 487]. 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 [420, 441]. In severe corporal fibrosis, semi-rigid prosthetic devices are preferable to inflatable implants [481, 488] (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 [489] (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.	B
Treatment aims to restore painless penile flaccidity, in order to prevent chronic damage to the corpora cavernosa.	C
Erectile function preservation is directly related to the duration of ischaemic priapism.	B
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 3-5 minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within 1 hour. Patients at high cardiovascular risk should be given lower doses. Patient monitoring is highly recommended.	B
The efficacy of shunt procedures for ischaemic priapism is questionable. Diagnose muscle necrosis when needed with cavernous biopsy. No clear recommendation on one type of shunt over another can be given.	C
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.	B

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 alkalisation 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 [420, 437, 438, 490, 491]. The most frequent cause of high-flow priapism is blunt perineal or penile trauma [81]. 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 [491]. This unregulated flow results in a persistent erection, and has been proposed to occur via a mechanism that involves stimulation of endothelial nitric oxide synthase by the turbulent blood flow [492]. Partial erections are enhanced after sexual stimulation, as the trabecular smooth muscle fully relaxes, activating the corporal veno-occlusive mechanism [491, 493].

There is often a delay between the injury and the development of the priapism that may be up to two to three weeks [493]. 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 [494, 495], with acute spinal cord injury [496] and occasionally following intracavernous injections or aspiration due to a lacerated cavernous artery or branch [497, 498]. Under these circumstances, it may complicate low-flow priapism. It has also been reported to occur following internal urethrotomy [499] and a Nesbit procedure [500]. Although sickle cell disease is usually associated with low-flow priapism, occasional cases of high-flow priapism have been reported [501].

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 [420]. 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 [435-437] (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 [502, 503]. However, due to its invasiveness it should be reserved for the management of arterial priapism, when embolisation is being considered [420, 433] (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 [504].

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 [420, 433] (LE: 3).

3.4.2.4.1   Conservative management
This may include applying ice to the perineum or site-specific perineal compression [437, 490, 505, 506]. It is an option in all cases, particularly children [507a] (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 [507b]. 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 alpha-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 [508-510], gel foam or sponge [509, 511], or more permanent substances, such as coils [509, 511-513] or acrylic glue [514] (LE: 3). Success rates of up to 89% have been reported [515] 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 [420, 516].

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 [436]. If there is doubt, a repeat arteriogram is required. Recurrence rates of 7-27% after a single treatment of embolisation have been reported [509, 510, 517] (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 [517, 518] (LE: 3).

Embolisation in children, although reportedly successful, is technically challenging and requires treatment within a specialist paediatric vascular radiology department [445, 519].

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 [3, 434, 520]. 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	GR
Because high-flow priapism is not an emergency, perform definitive management at the discretion of the treating physician.	B
Conservative management with the use of ice applied to the perineum or site-specific perineal compression may be successful particularly in children. The use androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	C
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.	B
Repeat the procedure for the recurrence of arterial priapism following selective artery embolisation.	B
Reserve selective surgical ligation of the fistula as a last treatment option when embolisation has failed.	C

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 [7, 521]. However, recurrent priapism episodes are common in men with sickle cell disease (42-64%) [522, 523] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [7].

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 [487].

Recently, several studies have proposed alternative mechanisms including inflammation, cellular adhesion, nitric oxide metabolism, vascular reactivity and coagulation [420, 429, 457, 524, 525].

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 [457, 524]. 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 [3]. 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 [428, 457, 524].

3.4.3.4.1   Alpha-adrenergic agonists
Studies of oral α-adrenergic agonists have suggested some benefit for daily dosing of these agents as effective prevention [526]. Side-effects include tachycardia and palpitations. Pseudoephedrine, widely used as an oral decongestant, can also be used as a first-line treatment [454]. However, its effect on corporal smooth muscle is not fully understood. Etilefrine 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% [10, 527, 528]. In one randomised, placebo-controlled, clinical study looking at medical prophylaxis with etilefrine 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 [428, 457, 529]. This can be done through the use of gonadotropin-releasing hormone (GnRH) agonists or antagonists, antiandrogens or oestrogens [530] (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-alpha-reductase inhibitors [531] (LE: 3) and ketoconazole, an antifungal agent that reduces adrenal and testicular androgen production [529, 532] (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 prepubertal boys, adolescents or men who are trying for 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 [428, 457, 533]. 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 [457]. 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 [533] (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 beta-agonist that causes vasodilation, resulting in smooth muscle relaxation of the vasculature [428, 457] and has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [45] (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 [455] (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 [529], and reduces testosterone- and follicle-stimulating hormone levels [534]. It is given at a dose of 400 mg, four times a day, up to 2400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of gabapentin, 300 mg daily [535] (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 [428]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal baclofen dosing is more effective [457, 536-538] (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 [529, 539]. It is an established treatment for ameliorating sickle cell disease and improving their life expectancy [456, 540]. For such patients with recurrent priapism there is limited evidence to suggest a medical prophylactic role (LE: 3) [529, 539, 541]. Side-effects include oligozoospermia and leg ulcers.

3.4.3.4.8 Phosphodiesterase type 5 inhibitors (PDE5Is)

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 [428, 457, 542-546] (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). PDE5Is 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 nitric oxide pathway, with down-regulation of cavernosal PDE5 thereby preventing the complete degradation of cGMP in the corpora cavernosa [428, 457, 542, 545].

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 [428, 457]. The most commonly used drugs are phenylephrine and etilephrine (as described in the treatment of ischaemic priapism) [3, 420, 521, 528] (LE: 3). Side-effects include hypertension, coronary ischaemia and cardiac arrhythmias.

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the proenzyme 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 [529, 547] (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	GR
The primary goal in the management of patients with stuttering priapism is the prevention of future episodes, which can generally be achieved pharmacologically.	B
PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease associated priapism.	C
The evidence with other systemic drugs (digoxin, alpha-adrenergic agonists, baclofen, gabapentin, terbutaline) is very limited.	C

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.

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5. CONFLICT OF INTEREST

EAU Guidelines on Male Infertility

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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 specialists who are initially responsible for assessing the male 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.

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 2015 the text was significantly reduced so that only key information was included and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

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 [1-4]. A separate scientific paper on Vasectomy was published in 2012 [4]. All texts can be viewed and downloaded for personal use at the society website: http://www.uroweb.org/guidelines/online-guidelines/.

1.3 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.

2. METHODS

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. 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 2016 print a scoping search was performed, covering all areas of the guideline, starting from the last cut-off date September 2013, covering 2014 with a cut-off date of January 2015. Embase, Medline and the Cochrane Central Register of Controlled Trials databases were searched, with a limitation to reviews, meta-analysis or meta-analysis of randomized controlled trials.. A total of 609 unique records were identified, retrieved and screened for relevance, of which about 10 publications were selected for inclusion.

2.1 Review

This document was subject to peer review prior to publication in 2015. The decision to 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.

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) [5].

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 [6]. Infertility affects both men and women. In 50% of involuntarily childless couples, a male-infertility-associated factor is found together 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 [5]. Male fertility can be reduced as a result of [5]:
*   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 spermiogram (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 [7]

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
All	100%	11.2%
Infertility of known (possible) cause	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
Idiopathic infertility	30.0	13.3
Hypogonadism	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
Others	0.8	0.8
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
General/systemic disease	2.2	0.5
Cryopreservation due to malignant disease	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
Disturbance of erection/ejaculation	2.4	-
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (CBAVD)	0.5	3.1
Others	0.8	1.9

CBAVD = Congenital Bilateral Absence of the Vas Deferens

3.2 Recommendations on epidemiology and aetiology

Recommendations	GR
To categorise infertility, investigate both partners simultaneously.	C
In the diagnosis and management of male subfertility, include the fertility status of the female partner 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 and
- age and fertility status of female partner.

The cumulative pregnancy rate is 27% in infertile couples with 2 years of follow-up and oligozoospermia as the primary cause of infertility [8]. Female age is the most important single variable influencing outcome in assisted reproduction [9]. 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) [10] 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.) [11]. 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
* varicocele.

5.1.2.1 Semen analysis

In NOA, semen analysis shows normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3000 g for 15 min and a thorough microscopic examination by phase contrast optics at ×200 magnification of the pellet. All samples can be stained and re-examined microscopically [11].

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 normal testis volume and still be azoospermic [13, 14].

5.1.2.3 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. Most authors therefore recommend taking several testicular samples. 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 increases retrieval rates vs. conventional TESE, and should be preferred in severe cases of non-obstructive azoospermia [18-21]. Positive retrievals are reported even in conditions such as Sertoli cell only syndrome type II [12].

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) [22-26]. Birth rates are lower in NOA vs. OA (19% vs 28%) [27, 28].
- 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 [29]
- 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 [30]

5.1.3 *Summary of evidence and recommendations*

Summary of evidence	LE
The WHO laboratory manual proposes reference values based on fertility hence, these reference values do not allow classifying a man as being infertile.	2a
Impaired spermatogenesis is often associated with elevated FSH concentration.	3
For patients with NOA who have spermatozoa in their testicular biopsy, 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 - also when testing for genetic abnormalities was negative.	A
In men with NOA, perform simultaneous testicular biopsy with multiple TESE (or micro TESE) to define spermatogenesis and diagnose ITGCNU.	A

ICSI = intracytoplasmic sperm injection; ITGCNU = intratubular germ cell neoplasma of unclassified type; TESE = testicular sperm extraction; NOA = non-obstructive azoospermia.

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 [31].

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 11 publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% [32]. 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 [32]. 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 [33, 34]. 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) [34]. A recent study proposes to restrict karyotype to NOA men with the purpose to prevent adverse pregnancy outcomes [35]. 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 [36]. 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 [37]. 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 [38].

The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism [39, 40] and in 1.36-25% of men with somatic karyotype 47,XXY [41-44]. In patients with azoospermia, TESE or (micro-TESE) can be proposed as a therapeutic option since spermatozoa can be recovered in about 30% of cases. 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 [36]. 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%) [44]. 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 [45].

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.

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 [32, 46-48] and with translocations [49]. Florescence *in situ* hybridisation analysis of spermatozoa is only indicated for specific andrology conditions e.g. macrocephalia [48].

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 [48, 49].

Spermatogenesis can be relatively easily induced by hormonal treatment [50], 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 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 [51-54] or fertile [55] 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 [56]. Nevertheless, to date only a few genes have been screened in relatively small populations and none of them appear relevant for male infertility [57, 58]. 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 [59, 60].

5.2.3 **Y-chromosome and male infertility**

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc [61]. 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 [62]. In each AZF region, there are several spermatogenesis candidate genes [63]. 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 [64].

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 [65].
- 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 [62].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [62].

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 [66].

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 [66], but occasionally the son has a larger one [67]. 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 [68, 69], 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 [70]. Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal [62, 66]. 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 [71]. 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 [66, 72-74]. 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 [73, 74]. 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 [75]. However, these data need further confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noticing that partial AZFc deletions (gr/gr and b2/b3) may predispose to complete AZFc deletion in the next generation [76, 77].

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 and considering 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 [78]. 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 [79, 80]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [75], 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%.

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 [81]. 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 with ipsilateral absence of the kidney, to bilateral vessel abnormalities and renal abnormalities, such as pelvic kidney [82].

5.2.4.2 Unknown genetic disorders
Considering the high predicted 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 [57]. 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 [57, 83, 84], and references therein. The introduction of new analytical approaches provided evidence for the importance of CNVs [59, 60] 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 [85-87].

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 [88].

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 preimplantation 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 deletion will be obligatorily 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 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 ICSI is used because spermatogenesis should be normal.	A
Inform men with Yq microdeletion and their partners who wish to proceed with 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 CFTR gene mutations.	A

CFTR = transmembrane conductance regulator; IVF = in vitro fertilisation; OA = obstructive azoospermia; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; TESE = testicular sperm extraction; CF = cystic fibrosis.

5.3 Obstructive azoospermia

Obstructive azoospermia (OA) is the absence of spermatozoa and spermatogenetic 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 [89]. 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 [89-93]. Congenital epididymal obstruction usually manifests as CBAVD, which is associated with at least one mutation of the CF gene in 82% of cases [92]. Congenital forms of epididymal obstruction include chronic sinopulmonary infections (Young's syndrome) [94]. Acquired forms secondary to acute (e.g., gonococcal) and subclinical (e.g., chlamydial) epididymitis are most common [95, 96]. Other causes may be trauma or surgical intervention [97, 98].

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 [1, 100]. 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 [101] (see Chapter 5.2).

5.3.1.4 Ejaculatory duct obstruction
Ejaculatory duct obstruction is found in 1-3% of cases of OA [89] 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 [102], while in Mullerian duct anomalies, the ejaculatory ducts are laterally displaced and compressed by the cyst [103]. Paramedian or lateral intraprostatic cysts are rare [104]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to urethroprostatitis [105]. 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) [105, 106].

5.3.1.5   Functional obstruction of the distal seminal ducts
Functional obstruction of the distal seminal ducts might be attributed to local neuropathy [107]. This abnormality is often associated with urodynamic dysfunction. Impaired sperm transport may be idiopathic or associated with 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 (4.2).

5.3.2.2   Clinical examination
Clinical examination should follow suggestions for the diagnostic evaluation of infertile men. The following findings indicate OA:
- 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 2-3 months, according to the WHO (see Chapter 3A.2). Azoospermia means the inability to detect spermatozoa after centrifugation at ×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 may 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 [93].

5.3.2.5   Ultrasonography
In addition to physical examination, a scrotal ultrasound 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. Invasive diagnosis, including testicular biopsy, scrotal exploration, and distal seminal duct evaluation, are indicated in patients with OA in whom an acquired obstruction of the seminal ducts is suspected. Explorative and recanalisation surgery should be carried out simultaneously.

5.3.2.6   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) [108] is indicated in men with CBAVD. TESE and PESA are also viable options [109]. Usually, one MESA procedure provides sufficient material for several ICSI cycles [110] and it produces high pregnancy and fertilisation rates [111]. In patients with azoospermia due to acquired epididymal obstruction, microsurgical reconstruction is recommended, with the preferred technique

being microsurgical intussusception tubulovasectomy [112]. Anatomical recanalisation following surgery may require 3-18 months. Before microsurgery (and in all cases where recanalisation is impossible), epididymal spermatozoa should be aspirated and cryopreserved for use in ICSI [110]. Patency rates range between 60% and 87% [98, 113] and cumulative pregnancy rates between 10% and 43%. Recanalisation success rates may be adversely affected by preoperative and intraoperative findings.

5.3.3.3 Proximal vas obstruction
Proximal vas obstruction after vasectomy requires microsurgical vasectomy reversal (see Chapter 3G). Vasovasostomy is also required in rare cases of proximal vasal obstructions. The absence of spermatozoa in the intraoperative 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 [114]. In these cases TESE/ MESA or proximal vas deferens sperm aspiration [115] 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) [105] can be used in large postinflammatory 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 [105]. Intraoperative 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 [116].

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
For azoospermia caused by vasal or epididymal obstruction, perform microsurgical vasovasostomy or tubulovasostomy.	B
Use sperm retrieval techniques, such as MESA, TESE, and 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 [12] 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 ultrasound investigation and colour Duplex analysis [12]. 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 [117]. 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 [118]. Varicocelectomy can reverse sperm DNA damage [119].

5.4.3.2   *Varicocelectomy*
Varicocele repair has been a subject of debate for several decades. A meta-analysis of randomised controlled trials and observational studies showed that surgical varicocelctomy significantly improves semen parameters in men with abnormal semen, but only in men with a clinical varicoceles [118].

In randomised controlled studies varicocele repair in men with a subclinical varicocele was found to be ineffective in increasing the chance of spontaneous pregnancies [120]. Also, in randomized studies that included mainly men with normal semen parameters no benefit was found in favour of treatment over observation [121]. A Cochrane review from 2013 concluded that there is evidence suggesting that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of pregnancy. In a subgroup analyses of five RCT's comparing treatment to observation in men with a clinical varicocele, oligospermia and otherwise unexplained infertility the analyses favoured treatment, with a combined OR 2.39 (95% CI 1.56 to 3.66) [122].

5.4.3.3   *Prophylactic Varicocelectomy*
In adolescents with a varicocle there is a significant risk of overtreatment since most adolescents with a varicocele will have no problem achieving pregnancy later in life [123]. Prophylactic treatment is only advised in case of documented growth deterioration of the testis documented by serial clinical examinations and in case of 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 [123]. Microsurgical repair has resulted 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	[124]	9	Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema
Retrograde sclerotherapy	[125]	9.8	Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation
Retrograde embolisation	[126, 127]	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
Open operation			
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele
Inguinal approach	[128]	13.3	Possibility of missing out a branch of testicular vein
High ligation	[129]	29	5-10% incidence of hydrocele (< 1%)
Microsurgical inguinal or subinguinal	[130, 131]	0.8-4	Post-operative hydrocele arterial injury, scrotal haematoma
Laparoscopy	[132, 133]	3-7	Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis; bleeding; postoperative 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 overtreatment: 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. [7].

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 [134]. 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 [134] and should be screened prior to assisted reproduction [135]. 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 or urinary FSH or human menopausal gonadotropins (HMGs) [136]. If hypogonadotropic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is pulsatile GnRH [137]. In patients who have developed hypogonadism before puberty and have not been treated with gonadotropins or GnRH, 1-2 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 FSH level is elevated. However, it has been reported that men with infertility are at higher risk for developing impaired Leydig cell function [138], while men with Klinefelter's syndrome often show high LH values and develop hypoandrogenism with ageing [139]. 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 [140]. Laboratory diagnosis of Hypergonadotropic hypogonadism is based on a high level of FSH, decreased serum testosterone, and increased LH levels [135]. 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 in oestradiol by the enzyme aromatase [141]. Anti-oestrogens and aromatase inhibitors may help in these patients elevating FSH and LH and potentially increase sperm quality, next to weight reduction. Injectable, oral and transdermal testosterone preparations are available for clinical use [135]. See also EAU Guidelines on Male Hypogonadism [142].

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 (hCG/hMG/rFSH).	A*
Do not use testosterone replacement for the treatment of male infertility.	A*

Upgraded following panel consensus.
FSH = follicle-stimulating hormone; LH = luteinising hormone.

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 [143]. Approximately 30% of undescended testes are non-palpable 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 [144].

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 vary, depending on the position of the testis [145]. 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 18 months the latest) to conserve spermatogenesis and hormone production, as well as to decrease the risk for tumours [146]. Surgical treatment is the most effective. Medical treatment with GnRH may be beneficial but long-term follow-up data are awaited. 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 [147].

5.6.1.1.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism [148]. Early surgical treatment may have a positive effect on subsequent fertility [149]. 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%.

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 [150]. 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 [151].

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 [152]. In adulthood, 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 [153]. 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 postoperative atrophy rate was 12% in those cases with long vascular pedicles that enabled scrotal positioning. Postoperative atrophy in staged orchidopexy has been reported in up to 40% of patients [154]. At the time of orchidopexy performed in adulthood testicular biopsy for detection of ITGCNU (formerly CIS) 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 [155]),

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 ITGCNU (formerly CIS).	B

ITGCNU = intratubular germ cell neoplasia of unclassified type.

5.7   Idiopathic male infertility
No demonstrable cause of infertility is found in at least 44% of infertile men [156].

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 [157]. 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 [158]. Androgens, bromocriptine, alpha-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. Gonadotrophins (hCG/HMG/rFSH) might be beneficial in regards to pregnancy rates and live birth in idiopathic male factor subfertility [159]. Men taking oral antioxidants had an associated significant increase in sperm parameters [160] and in live birth rates in IVF patients in a Cochrane analysis [161]. Concerning natural conception the role of antioxidants needs further investigations [162].

5.7.2   Recommendation for idiopathic male infertility

Recommendation	GR
Use medical treatment of male infertility only for cases of hypogonadotropic hypogonadism.	A
No 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 [163]. 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 [164]. 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 [165]. Various contraceptive regimens have been developed and tested, including testosterone monotherapy, androgen/progestin combinations, testosterone with GnRH analogues, and selective androgen- and progestin-receptor modulators [166]. 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 [167].

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 [3]. 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 [169].

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 [170, 171]. The most effective occlusion technique is cauterisation of the lumen of the vas deferens and fascial interposition [172-174]. 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 [168, 175]. Acute local complications associated with vasectomy include haematoma, wound infection, and epididymitis in up to 5% of cases [168]. The potential long-term complications (e.g., chronic testicular pain) [176] 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% [177]. However, patients should be informed preoperatively that, although rare, long-term recanalisation might occur [178]. No motile spermatozoa should be detected 3 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 [179].

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 [180].

- Vasectomy involving cauterisation and fascial interposition appears to be the most effective technique in the prevention of early recanalization [172, 177, 181].

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 [182].

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 is the pregnancy rate. 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 3 years after vasectomy; 88% and 53% for 3-8 years, 79% and 44% for 9-14 years, and 71% and 30% for > 15 years [183].

5.8.3.2 Tubulovasostomy
The chance of secondary epididymal obstruction after vasectomy increases with time. After an interval of 10 years, 25% of men appear to have epididymal blockage. If secondary epididymal obstruction occurs, tubulovasostomy is needed to reverse the vasectomy (see Chapter 3.4) [184].

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 [76, 109, 185, 186]. 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 the male contribution to 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
Vasectomy is the gold standard for the male contribution to permanent contraception.	A
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, MESA/PESA/TESE - together with 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
MESA = microsurgical epididymal sperm aspiration; PESA = percutaneous epididymal sperm aspiration;
TESE = testicular sperm extraction; ICSI = intracytoplasmic sperm injection.

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 [12, 187, 188]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [12]. 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 (CPPS) (NIH IIa vs. NIH 3B).

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 [189]. The ideal diagnostic test for Chlamydia trachomatis in semen has not yet been established [190]. 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 [190]. 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 [191]. Normal colonisation of the urethra hampers the clarification of mycoplasma-associated urogenital infections, using samples such as the ejaculate [192].

5.9.2.3   White blood cells
The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [193]. 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 [194]. According to 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 [195, 196]. 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 [188]. All investigations have given contradictory results, and have not confirmed that chronic prostatitis has a decisive role in altering conventional semen parameters [197-199].

5.9.2.5   Seminal plasma alterations
Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [188, 200, 201], with a suggested cut-off level of approximately 600 ng/mL [186]. 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 [202-204], 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 [205]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion (EPS) [206].

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 [188]. Reduced fructose concentration indicates impaired vesicular function [191, 207].

5.9.2.7   Reactive oxygen species
Reactive oxygen species might be increased in chronic urogenital infections associated with increased leukocyte numbers [208]. However, their biological significance in prostatitis remains unclear [188].

5.9.2.8   Disease management
Treatment of chronic prostatitis is usually targeted at relieving symptoms [209, 210]. 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 [211].

Only antibiotic therapy of chronic bacterial prostatitis (NIH II) 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 [211], there is no evidence that treatment of chronic prostatitis increases the probability of conception [188, 212].

*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* [213, 214]. 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 [215].

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 [213, 216, 217]. 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 [218].

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 *N. gonorrhoeae* or *C. trachomatis* 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 non-seminomas are preceded by CIS, and untreated ITGCNU will eventually progress to invasive cancer [219, 220]. The most convincing evidence for a general decline in male reproductive health is the increase in testicular cancer seen in western countries [221, 222]. In almost all countries with reliable cancer registers, the incidence of testicular cancer has increased [62, 223]. 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 dysgenic testes have an increased risk of developing testicular cancer in adulthood. These cancers arise from premalignant gonocytes or CIS cells [224]. Testicular microlithiasis (TM), seen on ultrasound, 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 [225]. 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 [226]. In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [227]. 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 [228]. The risk of hypogonadism is most pronounced in TGCT patients treated with ≥ 3 cycles of chemotherapy or irradiation of retroperitoneal lymph nodes. However, this risk is greatest at 6-12 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 2 years follow-up [219]. The risk of low libido and erectile dysfunction is also increased in TGCT patients [229]. In case of azoospermia, testicular sperm may be recovered to safeguard patient's fertility (Onco-TESE) [230].

5.10.3 *Testicular microlithiasis*
Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular ultrasound [231-233]. Although the true incidence of microcalcification in the general population is unknown, it is probably rare. However, ultrasound 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 ultrasound machines [234]. 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% [235-237]. 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 [238]. 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 ultrasound, 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 [222].

5.10.4 *Recommendations for germ cell malignancy and testicular microcalcification*

Recommendations	GR
As for all men, encourage patients with TM and without special risk factors (see below) to perform self-examination because this might result in early detection of TGCT.	B
Do not perform testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic 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: infertility 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

TM = testicular microlithiasis; TGCT = testicular germ cell tumour; CT = computed tomography.

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 [239]. 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 [240] (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 [239]. 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 [241] or iatrogenic penile nerve damage [242]), or pharmacological (e.g. selective serotonin re-uptake inhibitors (SSRIs), antihypertensives, or antipsychotics) [243].

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	α1-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 verumontaneum hyperplasia prostate)	Bladder neck resection (transurethral resection of the
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 [243]. 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, EPS, 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 [244].

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 [245]. Treatment should be given for urogenital infections (i.e., in case of painful ejaculation) [244]. Dapoxetin is an SSRI that has been introduced for the therapy of PE [246], 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 [247].

Table 7: Drug therapy for retrograde ejaculation

Drug	Dosage regimen	Ref.
Ephedrine sulphate	10-15 mg four times daily	[248]
Midodrine	5 mg three times daily	[249]
Brompheniramine maleate	8 mg twice daily	[250]
Imipramine	25-75 mg three times daily	[251]
Desipramine	50 mg every second day	[252]

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 [253], 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 [254]. When electro-ejaculation fails or cannot be carried out, sperm can be retrieved from the seminal ducts by aspiration from the vas deferens [255] (see Chapter 3D) or seminal tract washout [256]. TESE can then be used [244, 257]. Anejaculation following either surgery for testicular cancer or total mesorectal excision can be prevented using monolateral lymphadenectomy or autonomic nerve preservation [257], 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 premature ejaculation) or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing. Alternatively use topical anesthetics (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 ART.	B
To treat disorders of ejaculation, offer pharmacological treatment of 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.	A
Alternatively offer topical anaesthetics or tramadol.	A

ART = assisted reproduction technique; SSRIs = selective serotonin reuptake inhibitors.

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 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 or for non-malignant diseases [258].
- 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 [259-262]. Further damage can be caused by contamination of samples with microorganisms and high levels of superoxide radicals [263, 264]. 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 [265, 266]: sample is held in the vapour phase for 10 min before being plunged into liquid nitrogen.
- Slow or multi-step method [267]: sample is gradually cooled in the vapour phase for approximately 40 min. A programmable automatic freezing machine, which is preset to cool at a rate of 1-10°C/min 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 [268] or in a container [269].

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 [270]. 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 double-wrapping 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 [271] and morphology [272, 273] 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 [266]. 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 [268].

*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 techniques 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. It must not be stored in the same container as samples from men who have been tested and are free from infection.	C

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7.   CONFLICT OF INTEREST

All members of the EAU Male Infertility 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. 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

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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, bone health, and behaviour. Low levels of circulating androgens in utero can cause disturbances in male sexual development, resulting in congenital abnormalities of the male reproductive tract. Later in life, this may cause reduced fertility, sexual dysfunction, decreased muscle formation and bone mineralisation, disturbances of fat metabolism, and cognitive dysfunction. Testosterone levels decrease slightly as a process of ageing: signs and symptoms caused by this decline can be considered a normal part of ageing. However, low testosterone levels are also associated with obesity and several chronic diseases, and some symptomatic 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 hypogonadism and ageing-related decline in testosterone in male patients, 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.

1.2   Publication history

The present Male Hypogonadism Guidelines are a revision 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 and clinical andrologists.

2.   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. 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 the current guidelines are based on a systematic literature search and review performed by the panel members in 2014. 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'. All articles published before November 2014 were considered for review. The expert panel reviewed these records and selected articles with the highest level of evidence in accordance with a rating schedule adapted from the Oxford Centre for Evidence-Based Medicine levels of evidence.

2.1   Review

This document was subject to peer review prior to publication in 2015. The decision to 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.

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) [1].

Androgen deficiency increases slightly with age also in healthy men [2, 3]. In middle-aged men, the incidence of biochemical hypogonadism varies from 2.1-12.8% [4]. The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 varies form 2.1-5.7% [3, 4]. 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 [5].

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 located on the short arm of the Y chromosome, including the sex-determining region of the Y chromosome (SRY gene complex) and the SOX gene on chromosome 17 [6]. 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. AMH activity results in regression of the Müllerian ducts (Figure 1). INSL3 and AMH regulate testicular descent.

Under the influence of intratesticular testosterone, the number of gonocytes per tubule increases threefold during the foetal period [7]. 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 5α-dihydrotestosterone (DHT) by the enzyme 5α-reductase. Testosterone and DHT are required for penile growth, both activating the androgen receptor [8].

Intratesticular testosterone is needed to maintain the spermatogenic process and to inhibit germ cell apoptosis [9]. 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 [10]. Complete inhibition of intratesticular testosterone results in full cessation of meiosis up to the level of round spermatids [11, 12]. 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 [11]. 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 [13]. The production of testosterone is controlled in the foetus by placental choriongonadotropin (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 [14]. Figure 1 shows the development of the male reproductive system.

3.2.1 The androgen receptor

Testosterone exerts its action through the 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 [8, 13]. 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 [15]. 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

[15]. The AR CAG repeat length is inversely correlated with serum total and bioavailable testosterone and oestradiol in men. Shorter repeats have been associated with an increased risk for prostate disease, and longer repeats with reduced androgen action in several tissues [16]. CAG repeat number may influence androgenic phenotypical effects, even in case of normal testosterone levels [17].

Summary of evidence
Testosterone is essential for normal male development.

Figure 1: Development of the male reproductive system
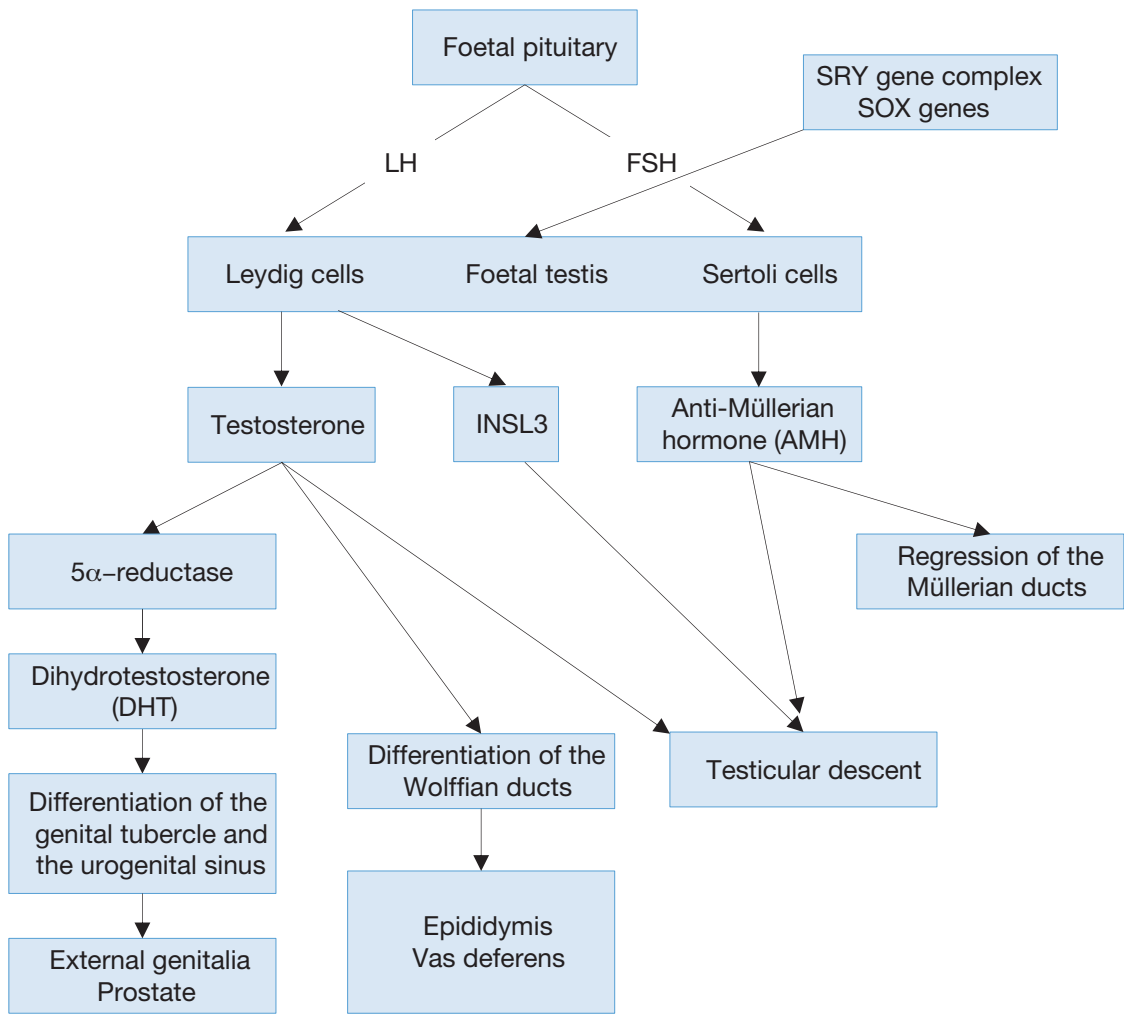
FSH = follicle-stimulating hormone; LH = luteinising hormone; SRY = sex determining region of the Y chromosome; INSL3= insulin-like peptide 3.

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. The most important 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,XXX in 90% of cases [18]. It arises due to non-disjunction during paternal or maternal meiotic division of germ cells [19].
- 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 [20-22].

The main reasons for primary testicular failure 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-antagonistic effects of substances such as phenothiazine, imipramine, risperidone and metoclopramide); additional causes may be chronic renal failure or hypothyroidism.
- *Isolated* (formerly termed idiopathic) hypogonadotrophic hypogonadism (IHH).
- *Kallmann syndrome* (hypogonadotrophic hypogonadism with anosmia, genetically determined, prevalence one in 10,000 males).

These disorders are characterised by disturbed hypothalamic secretion or action of gonadatropin-releasing hormone (GnRH), as a pathophysiology common to the diseases, resulting in impairment of pituitary LH and FSH secretion. An additional inborn error of migration and homing of GnRH-secreting neurons results in Kallmann syndrome [23, 24]. The most important symptom is the constitutional delay of puberty: it is the most common cause of delayed puberty (pubertas tarda) [25]. 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*

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 been labelled as late-onset hypogonadism and age-related hypogonadism is comprised of three types of hypogonadism and formally secondary hypogonadism is the most prevalent [26, 27]. It should however be stated that low testosterone and low gonadotropin levels do not exclude a compromised gonadal response to LH stimulation as has been demonstrated in obesity, corticosteroid induced hypogonadism etc.

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 5α-reductase deficiency (for a review, see Nieschlag *et al.* 2010) [28].

The classification of hypogonadism has therapeutic implications. In patients with secondary hypogonadism, hormonal stimulation with human chorionic gonadotropin (hCG) and FSH or alternatively pulsatile GnRH treatment can restore fertility in most cases [29, 30]. 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.
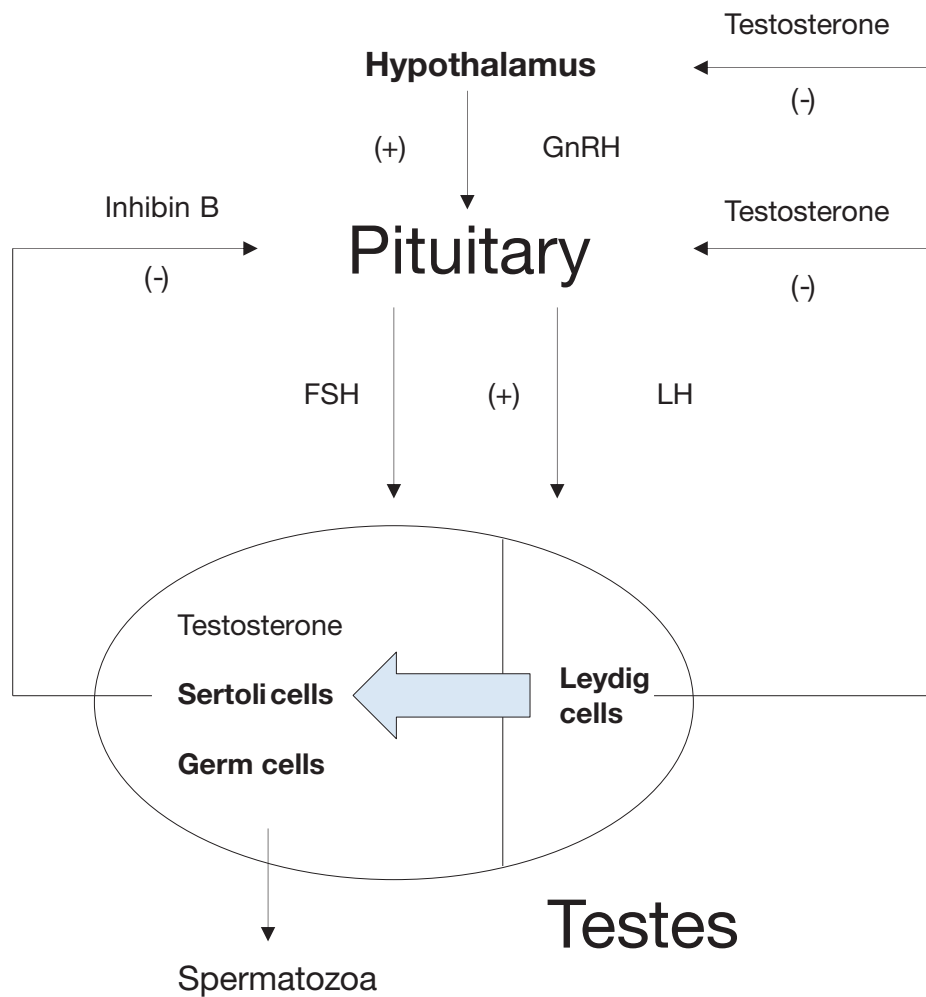
Table 1: Most common forms of primary hypogonadism

Disease	Causes of deficiency
Maldescended or ectopic testes	Failure of testicular descent, maldevelopment of the testis
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
(Idiopathic) testicular atrophy	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
Klinefelter syndrome 47,XXX	Sex-chromosomal non-disjunction in germ cells
46,XY disorders of sexual development (DSD) (formerly male pseudohermaphroditism)	Disturbed testosterone synthesis due to enzymatic defects of steroid biosynthesis (17,20- lyase defect, 17β-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 [31]

Table 2: Most common 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, IHH)	Specific (or unknown) mutations affecting GnRH synthesis or action
Kallmann 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 tothe 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) (LH 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

Testosterone

Hypothalamus

(-)

(+)   GnRH

Inhibin B   Testosterone

Pituitary

(-)   (-)

FSH   (+)   LH

Testosterone

Sertoli cells   **Leydig cells**

Germ cells

Testes

Spermatozoa

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 [4, 32-35].

4.1   Clinical symptoms
Low levels of circulating androgens may be associated with signs and symptoms (Table 3) [4, 36, 37]

Table 3: Clinical symptoms and signs suggestive for androgen deficiency

Delayed puberty
Small testes
Male-factor infertility
Decreased body hair
Gynaecomastia
Decrease in lean body mass and muscle strength
Visceral obesity
Decrease in bone mineral density (osteoporosis) with low trauma fractures
Reduced sexual desire and sexual activity
Erectile dysfunction
Fewer and diminished nocturnal erections
Hot flushes
Changes in mood, fatigue and anger
Sleep disturbances
Metabolic syndrome
Insulin resistance and type 2 diabetes mellitus
Diminished cognitive function

The most prevalent symptoms of male hypogonadism in ageing men are reduced sexual desire and sexual activity, erectile dysfunction, and hot flushes [4, 37]. Other factors found associated with low testosterone were waist circumference and health status [4]. 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 recently been compiled from three large community-based samples, suggesting a cut-off of 12.1 nmol/L for total serum testosterone and for free testosterone 243 pmol/L, to distinguish between normal levels and levels possibly associated with deficiency [38]. Symptoms suggesting the presence of hypogonadism [4, 37] 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 [39]. 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 [40]. Both immunoassay and mass spectrometry based assays can produce valid 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.

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 subclinical 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.

4.2 History-taking and questionnaires
Symptoms of hypogonadism are listed in Table 3 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 primary hypogonadism. Adult-onset hypogonadism is characterised by sexual dysfunction, obesity and loss of vigour. Published questionnaires are unreliable and have low specificity, and they are not effective for case-finding [41-44]. 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 marihuana, opiates and alcohol and previous treatment or use of testosterone or abuse of anabolic steroids should also be included in history-taking.

4.3 Physical examination

Assessment of body mass index (BMI), the waist-hip ratio (or sagittal abdominal diameter), body hair, malepattern hair loss, presence of gynaecomastia and testicular size (measured with an orchidometer or ultrasound [US]) and a structural 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 (Table 3).	3	C
Measure testosterone in the morning before 11.00 hours 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: - 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: - Type 2 diabetes. - Metabolic syndrome. - Obesity. - Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region. - End-stage renal disease receiving haemodialysis. - 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 14 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 in phenotypic men or primary amenorrhoea in XY women.

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 14 [45]. 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 prepubertalonset hypogonadism is evident (Table 4) and diagnosis and treatment are fairly straightforward. The major challenge in younger individuals with presumed idiopathic 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 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 subfertility [46].

Table 4: Signs and symptoms suggesting prepubertal-onset hypogonadism

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*
Definition: 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 include: loss of libido, erectile dysfunction, sarcopenia, low bone mass, depressive thoughts, fatigue, loss of vigour, loss of body hair, hot flushes and reduced fertility (Table 3). Most of these symptoms have a multifactorial aetiology, are reminiscent of normal ageing and can also be found in men with completely normal testosterone levels [2]. As a result, signs and symptoms of adult-onset hypogonadism may be nonspecific, 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 [37, 47]. 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.

4.5.3.1 *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
In adult men with established hypogonadism, screen for concomitant 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 is to improve QoL, 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 therapy.

Table 5: Indications for testosterone treatment

Delayed puberty (idiopathic, Kallmann 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 4)
Hypopituitarism
Testicular dysgenesis and hypogonadism
Type 2 diabetes mellitus with hypogonadism

Table 6: Contraindications against testosterone treatment

Prostate cancer
Male breast cancer
Severe sleep apnoea
Male infertility-active desire to have children
Haematocrit > 0.54%
Severe lower urinary tract symptoms due to benign prostatic hyperplasia
Severe chronic cardiac failure/New York Heart Association Class IV

5.2   Benefits of treatment

In congenital hypogondotrophic 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 [29, 30].

In adult-onset hypogonadism Testosterone Replacement Therapy (TRT) 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 TRT.

TRT may present several benefits regarding body composition, metabolic control, psychological and sexual parameters. Randomised trials show a correlation between restored physiological testosterone levels, muscle mass and strength measured as leg press strength and quadriceps muscle volume [36, 48-50]. 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 [49, 51, 52]. Body composition is influenced by testosterone therapy in hypogonadal men, with a consequent decrease of fat mass and an increase in lean body mass [49]. Several studies based on testosterone undecanoate, demonstrate a significant reduction in trunk and waist fat with an evident decrease in waist size [53, 54]. In the same trials, testosterone undecanoate administration showed an improvement in body weight, body mass index and lipid profile after 3 months of therapy [53]. TRT presents positive effects in glycemic and lipid control, insulin resistance and visceral adiposity in hypogonadal men with impaired glucose tolerance and lipid profile with a consequent decrease in mortality [55, 56]. 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 [57-61].

Benefits on libido, erection and ejaculation have been reported in hypogonadal men in several retrospective studies and case reports: Small improvements in satisfaction with erectile function and moderate

improvements in libido have been shown by a meta-analysis of 17 placebo-control trials [49, 62-64]. In a recent multicenter prospective study a significant increase in the IIEF (International Index of Erectile Function) regarding sexual desire, intercourse satisfaction and overall satisfaction was reported, starting 6 weeks from the start of treatment [63]. TRT showed encouraging results in several studies, where satisfactory sexual intercourse was reported at least three months after therapy induction in hypogonadal men suffering from erectile dysfunction [49, 64]. Improvement of sexual symptoms will largely depend on the aetiology of the dysfunction: TRT in men with normal testosterone levels seems not very effective, but TRT may help improve response to phosphodiesterase type 5 (PDE5) inhibitors in hypogonadal men [65].

Significant improvement of depressive symptoms in men treated with testosterone undecanoate were reported in a recent randomised trial [66], as well as benefits in the cognitive spectrum [67]. Meta-analysis of data from randomised placebo-controlled trials has shown a significant positive impact of testosterone on mood [68]. Benefits in relation to the cognitive spectrum have been reported in studies with lower impact.

Summary of evidence	LE
Testosterone replacement therapy (TRT) may improve symptoms, but many hypogonadal men have a chronic illness and are obese: weight reduction, lifestyle modification and good treatment of comorbidities is more important than just TRT.	2
Testosterone replacement treatment can improve body composition, bone mineralisation, signs of the metabolic syndrome and male sexual problems.	3
A reduction in BMI and waist size, improved glycaemic control and lipid profile are observed in hypogonadal men receiving TRT.	2a

5.3 Choice of treatment

The aim of TRT is to restore physiological testosterone levels in hypogonadal men [69]. 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 [70]. 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 [71]. 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 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 [69]. 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 [72].

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 [73, 74]. They are also associated with increased rates of erytrocytosis.

5.3.1.3 Transdermal testosterone

Transdermal testosterone preparations are available as skin patches or gel. They provide a uniform and normal serum testosterone level for 24 hours (daily interval). Common side-effects consist of skin irritation at the site of application (patches) and risk of interpersonal transfer if appropriate precautions are not taken (gel) [75, 76]. The topical application of Testosterone 2% to the axillae is recently gaining more popularity: it 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 [77-79].

5.3.1.4 Sublingual and buccal testosterone

Sublingual and buccal testosterone tablets are effective and well-tolerated delivery systems that can provide a rapid and uniform achievement of a physiological testosterone level with daily administration [80, 81].

5.3.1.5   Subdermal depots
Subdermal depots need to be implanted every five to seven months and offer a long period of action without significant serum fluctuation of the testosterone level. The risk with this kind of delivery system lies in infections and extrusions, which may occur in up to 10% of cases [69, 82, 83].

5.4   Hypogonadism and fertility issues

Exogenous testosterone reduces endogenous testosterone production by negative feedback on the hypothalamic-pituitary-gonadal axis. If secondary hypogonadism coincides with fertility issues, hCG treatment should be considered, especially in men with low gonadotropins. hCG stimulates testosterone production of Leydig cells. Its administration should be restricted to patients with secondary hypogonadism, if fertility issues are important. 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 spermatogenesis in patients with secondary hypogonadism and fertility issues. 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 male hypogonadism, except in patients in whom fertility treatment is an issue.

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 [69]. 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 [73].
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 [72, 73].
Testosterone undecanoate	Intramuscular; one injection every 10-14 weeks	Steady-state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects [74].
Transdermal testosterone	Gel or skin patches; daily application	Steady-state testosterone level without fluctuation.	Skin irritation at the site of application and risk of interpersonal transfer [75, 76].
Sublingual testosterone	Sublingual; daily doses	Rapid absorption and achievement of physiological serum level of testosterone.	Local irritation [80, 81].
Buccal testosterone	Buccal tablet; two doses per day	Rapid absorption and achievement of physiological serum level of testosterone.	Irritation and pain at the site of application [80, 81].
Subdermal depots	Subdermal implant every five to seven months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants [69, 82, 83].

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 hCG treatment for hypogonadotrophic hypogonadal patients with simultaneous fertility treatment.	1b	B
In patients with adult-onset hypogonadism, only attempt testosterone treatment in men with major 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 TRT 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 [84]. The incidence is higher in men with Klinefelter syndrome. Testosterone treatment is contraindicated in men with a history of breast cancer [27]. Association between TRT and development of breast cancer is not supported by strong evidence although there are some reports based on small numbers of patients [85].

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 [86, 87]. Short-term randomised controlled trials support the hypothesis that TRT does not result in changes in prostatic histology nor in a significant increase in intraprostatic testosterone and DHT [88, 89]. Most recent studies indicate that testosterone therapy does not increase the risk of prostate cancer [88-91], but long-term follow-up data are not yet available. A recent meta-analysis showed a higher (but not statistically significant) percentage of prostate events in middle-aged and older men on TRT, but they were more likely to have a prostatic biopsy due to some increase in prostate-specific antigen (PSA), which is common in men on TRT [70].

Testosterone therapy is clearly contraindicated in men with advanced prostate cancer. A topic under debate is the use of TRT 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 [89]. According to a recent retrospective study on hypogonadal men with previous history of prostate cancer receiving TRT following cancer diagnosis, treatment was not associated with increased overall or cancer-specific mortality, but TRT was more likely to be prescribed in patients undergoing radical prostatectomy for well-differentiated tumours [92]. No randomised placebo-controlled trials are available yet to document its long-term safety in these patients [69]. 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 TRT [93-95]. 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; preoperative PSA < 10 ng/ml). Therapy should not start before one year of follow-up after surgery and patients should be without PSA recurrence [65, 94-96].

Patients who underwent brachytherapy or external beam radiation (EBRT) for low risk prostate cancer can also be cautiously considered for TRT in case of symptomatic hypogonadism with a close monitoring of prostate cancer recurrence [92, 94, 96, 97], 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, for cardiovascular disease and also for all-cause and cardiovascular mortality [98]. Endogenous testosterone levels within the mid-normal range are associated with the lowest risk of mortality [61].

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 [99, 100]. 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.

TRT has also in some studies demonstrated beneficial effects on certain cardiovascular risk factors [101]. In men with angiographically proven coronary disease those with low testosterone are at greater risk of mortality [102, 103]. Over many years since TRT 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 [104]. MACE is defined as the composite of cardiovascular death, nonfatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. However, three recent studies (one placebo-controlled trial [105] and two observational studies [106, 107] have suggested that TRT may be associated 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' [108]. These findings are supported by letters in response to the paper by Vigen *et al.* [109].

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.'

The TOM trial (Basaria *et al.*) used a testosterone dose twice that recommended for initiation of treatment, so does not reflect normal clinical practise, in addition the study was underpowered to detect an increased risk of cardiovascular events. 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 TRT and adverse cardiovascular events [58]. There are however no long-term studies or randomised controlled trials (RCT's) that provide a definitive answer. Observational studies have reported that TRT improves survival when compared to men who were not treated [56, 110]. These findings are supported by a large retrospective analysis of 6,355 men treated with TRT compared to 19,065 non-users which did not demonstrate any increased risk of myocardial infarction with TRT [111].

Caution should however be used in men with pre-existing cardiovascular disease. Firstly, hypogonadism must be carefully diagnosed beyond reasonable doubt. Secondly, if TRT is prescribed then testosterone levels should not exceed the mid-normal range and the haematocrit should not exceed 0.54. 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 value of > 54 is based on the increased risk of cardiovascular mortality from the Framingham Heart Study [112] which was recently confirmed in another study [113]. This value is also supported by the known increased risk of thrombosis in the congenital condition of idiopathic erythropoiesis [114]. The majority of patients with cardiovascular disease will be receiving anti-platelet therapy. An electrocardiogram prior to TRT in the assessment of hypogonadism could be considered.

Venous thromboembolism in one study of men on TRT reported 42 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. High endogenous levels of testosterone and/or estradiol are not associated with an increased risk of venous thromboembolism [115]. TRT 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 12 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 [48, 116, 117]. 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.

5.6.4 **Obstructive sleep apnoea**
There is no consistent evidence correlating TRT with obstructive sleep apnoea (OSA). There is also no evidence that TRT can result in the onset or worsening of the condition [118].

5.7   Summary of evidence and recommendations on risk factors in testosterone replacement treatment (TRT)

Summary of evidence	LE
Case reports and small cohort studies point to a possible correlation between TRT 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 TRT does not result in changes in prostatic histology.	1b
Recent studies indicate that testosterone therapy 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 TRT and obstructive sleep apnoea.	3
There is no substantive evidence that TRT, when replaced to the normal physiological range, is related to the development of major adverse cardiovascular events.	1a
In hypogonadal men TRT has been demonstrated to have a positive impact on cardiovascular risks [58].	1b

Recommendations	LE	GR
Perform haematological, cardiovascular, breast and prostatic assessment before the start of treatment.	1a	A
Monitor haematocrit, haemoglobin and PSA during TRT therapy.	3	A
Offer TRT 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; preoperative PSA < 10 ng/mL) and should not start before 1 year of follow-up.	3	B
Assess for cardiovascular risk factors before commencing TRT 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 TRT 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

PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

6.   FOLLOW-UP

6.1   Monitoring of patients receiving testosterone replacement therapy
Regular follow-up is needed in patients receiving testosterone therapy, as potentially androgen-dependent symptoms and conditions may occur as a result of TRT. The side-effects of TRT are limited, but their incidence and clinical relevance is as yet unclear. The primary aim of TRT 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 TRT on sexual interest may already appear after three weeks of treatment, and reach a plateau at six weeks [49]. Changes in erectile function and ejaculation may require up to six months [49]. Effects on QoL, and also on depressive mood, may become detectable within one month, but the maximum effect may take longer [49].

6.2   Testosterone level
There are as yet insufficient data to define optimal serum levels of testosterone during TRT. Expert opinion suggests that TRT 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 TRT used. It is

of importance to evaluate symptom regression and lack of response prompts termination of treatment and eventual reassessment of the diagnosis.

6.3 Bone density
Bone mineral density (BMD) should be monitored only in men whose BMD was abnormal before initiation of TRT. An increase in lumbar spine BMD may already be detectable after six months of TRT and may continue for three more years [49].

6.4 Haematocrit
It is important to use only minimal or no venous occlusion when taking a blood sample for haematocrit measurements [114]. Elevated haematocrit is the most frequent side-effect of TRT. The clinical significance of a high haematocrit level is unclear, but it may be associated with hyperviscosity and thrombosis [115]. The effect of erythropoiesis may become evident at three months and peaks at twelve months [49].

6.5 Prostate safety
TRT results in a marginal increase in PSA and prostate volume, plateauing at 12 months [49]. Previous fears that TRT might increase the risk of prostate cancer have been contradicted by a number of meta-analyses [70, 88, 89, 91]. However, there are insufficient long-term data available to conclude that there is safety from prostate cancer with TRT. 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 TRT can result in fluid retention and an exacerbation of the condition [116, 117]. 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 treatment at three, six and twelve months after the onset of treatment, and thereafter annually.	4	C
Monitor 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 PSA before the start of TRT. Follow-up by PSA at three, six and twelve months and thereafter annually.	4	C
Assess men with cardiovascular diseases for cardiovascular symptoms before TRT is initiated and continue close clinical assessment during TRT.	1b	A

BMD = bone mineral density; PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

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8. CONFLICT OF INTEREST

EAU Guidelines on Urological Infections

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**European
Association
of Urology**

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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 infections. These guidelines also aim to address the important public health aspects of infection control and antibiotic 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.

1.2 Panel composition

The EAU Urological Infections Guidelines Panel consists of an international group of urologists 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/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/urological-infections/

1.4 Publication history

The Urological Infections Guidelines were first published in 2001. *This 2016 document consists of the first completed sections of an entirely new Urological Infections Guideline formulated following new EAU guideline production methodology. Subsequent sections will be added over the next three years to cover the key clinical questions.* In the interim, the previous 2015 guidelines will be available through the EAU website Uroweb for sections not yet contained in the new guideline, http://uroweb.org/guideline/urological-infections/.

2. METHODS

2.1 Introduction

For the 2016 Urological Infections Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. All chapters were written 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-systematic-reviews.html.

Systematic review results for the following evidence questions are included in the 2016 Urological Infections Guidelines:

1. 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]?
2. In men with acute epididymitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?
3. Which technical or procedural strategies are effective for reducing infectious complications 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.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2017 update of the Urological Infections Guidelines.

Topics are:
1. What is the most effective management for people with asymptomatic bacteriuria?
2. In women with recurrent symptomatic lower urinary tract infection what interventions reduce the rate of recurrence?
3. What interventions reduce the rates of symptomatic urinary tract infection, bacteriuria and bacteremia in patients with urinary catheters?
4. What is the best antimicrobial prophylaxis strategy to reduce risk of infectious complication of prostate biopsy?
5. In men with symptoms of urethritis or men being screened for sexually transmitted infection what is the best method of detecting the causative pathogen?
6. In men with symptoms of urethritis what are the best treatment strategies for clinical or microbiological cure?
7. In urological patients with urosepsis what interventions improve outcomes?

3. ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship programmes aim to optimise the outcome of prevention and treatment of infection whilst curbing overuse and misuse of antimicrobial agents [6-10]. Measures of success include regulating antibiotic prescribing, and reduction in both the rate of healthcare associated infections such as *Clostridium difficile* and the emergence of resistant organisms [10]. In urology, antimicrobial stewardship programmes should include a series of measures to ensure rational, evidence based use of antibiotics in the prevention and treatment of infections of the urinary tract and male accessory glands, as well as non-antibiotic strategies. Programmes require a stewardship team approach comprising urologists, infectious diseases physicians, microbiologists and clinical pharmacologists or pharmacists [7-10].

The most important components of antimicrobial stewardship programmes are [8]:
- 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 antibiotic use when patient outcome is unlikely to be compromised [10, 11]. Studies specific to the urology setting are lacking but a case-control study showed reduction in antibiotic 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 [12].

4. DETECTION OF BACTERIURIA PRIOR TO UROLOGICAL PROCEDURES

4.1 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?

4.2 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 optimize 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 the Urological Infections Guidelines 2015 is recommended [13].

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.

4.3 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 [14-31]. None of the studies focused on a urology patient population.

4.3.1 Reagents strip (dipstick) urinalysis

Sixteen studies assessed dipstick urine analysis using a variety of criteria for a positive test [14-22, 25-27]. 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 [LE 2].

4.3.2 Automated microscopy

Two studies used automated microscopy of urine sediment following centrifugation [23, 27]. 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 [LE 2].

4.3.3 Dipslide culture

We found two studies on dipslide technology using different culture media [24, 31]. 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 [24]. Overall, dipslide technology is currently unsuited to routine use in this setting with further studies required to determine the best combination of culture media [LE 2].

4.3.4 Flow cytometry

We found no studies on this technology that met our inclusion criteria. The poor quality of available studies was confirmed in a recent meta-analysis [32].

In summary, laboratory urine culture remains the standard investigation to detect both the presence and absence of clinically relevant concentrations of bacteria in urine [LE 3].

4.4 Recommendation for the detection of bacteriuria prior to urological procedures

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

5.   ACUTE INFECTIVE EPIDIDYMITIS

5.1   Evidence question

In men with acute epididymitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?

5.2   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 [33]. 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 *Chlamydia trachomatis*, Enterobacteriaceae (typically *Escherichia coli*) and *Neisseria gonorrhoeae* [34]. 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.

5.3   Diagnostic Evaluation

Culture of mid-stream specimen of urine should be performed and any previous urine culture results should be checked. Sexually transmitted infection (STI) with *Chlamydia trachomatis* or *Neisseria gonorrhoeae* should be detected by nucleic acid amplification test (NAAT) on first voided urine. A urethral swab or smear should be performed for Gram staining and culture if *Neisseria 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 *Mycobactrium tuberculosis* DNA [35]. 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.

5.4   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 *Chlamydia 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 *Chlamydia trachomatis* and both achieve adequate levels in inflamed male genital tissues with oral dosing. Macrolide antibiotics such as azithromycin are effective against *Chlamydia 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 *Neisseria 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 3 days and men with likely or proven STI should be assessed at 14 days to check cure and ensure tracing and treatment of contacts according to local public health recommendations.

5.5   Evidence Summary

We found three guidelines based on systematic reviews [36-38] with search dates of December 2009, March 2012 and April 2013 respectively. Our 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 [39-43].
Data from a large comparative case series [LE 3] 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 [43].

Empiric antibiotic regimens [LE 3] from existing guidelines [36-38] 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 *Chlamydia trachomatis* and Enterobacteriaceae should be used. Appropriate options are:
     A.   A fluoroquinolone active against *Chlamydia trachomatis* by mouth once daily for 10 to 14 days*

                                    OR
     B.   Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for 10 to 14 days* *plus* an antibiotic active against Enterobacteriaceae** for 10 to 14 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 10 -14 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 10 to 14 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 [LE 3] found that lack of separation of epididymis and testis on palpation and the presence of abscess on ultrasound (US) may predict requirement for surgery following initial antibiotic treatment [39].

A cohort study [LE 4] found semen parameters may be impaired during epididymitis but recovered following successful treatment [42]. Comparative clinician cohort studies suggest adherence to guidelines for assessment and treatment of epididymitis is low, particularly by urologists compared to sexual health specialists [40] and by primary care physicians [41].

5.6   Recommendations for the treatment of acute infective epididymitis

Recommendations	LE	GR
Obtain a mid-stream urine and a first voided urine for pathogen identification.	3	A*
Initially prescribe a single antibiotic or a combination of two antibiotics active against *Chlamydia trachomatis* 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 *Chlamydia trachomatis*.	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 STI.	3	A*

* *Upgraded based on Panel consensus*

Figure 1: Diagnostic and treatment algorithm for adult men with acute epididymitis.

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                    ┌─────────────────────────┐
                    │ Acute scrotal pain and  │
                    │  swelling in adult male │
                    └─────────────────────────┘
                     ╱                       ╲
        ┌──────────────────┐         ┌──────────────────────┐
        │ Torsion suspected│         │ Suspected epididymitis│
        └──────────────────┘         └──────────────────────┘
                 │                      ╱              ╲
    ┌──────────────────────┐  ┌──────────────┐  ┌──────────────┐
    │ Urgent surgical      │  │  Gonorrhoea  │  │  Gonorrhoea  │
    │ exploration          │  │   unlikely   │  │    likely    │
    └──────────────────────┘  └──────────────┘  └──────────────┘
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Midstream urine for culture

Urethral swab/smear

First voided urine for nucleic acid amplification test (NAAT)

┌──────────────────────┐
│ Failure to respond or│
│ abscess present   │
└──────────────────────┘

Scrotal ultrasound examination Clinical Assesment

┌──┐   ┌──────────────────────────┐
│ Single antibiotic or a combination of │   │ Ceftriaxone 500mg IM   │
│ two antibiotics active against   │   │ plus a course of an   │
│ *Chlamydia trachomatis* and   │   │ antibiotic active against│
│ Enterobacteriaceae   │   │ *Chlamydia trachomatis* │
│   │   └──────────────────────────┘
│ Consider parenteral therapy if severe │
│ infection   │
└──┘

┌──┐
│ Proven sexually transmitted infection │
│ • Reporting   │
│ • Check cure   │
│ • Trace and treat contacts   │
└──┘

IM = Intramuscularly

6.   PROSTATE BIOPSY INFECTION: NON-ANTIBIOTIC PREVENTION

6.1   Evidence question
Which non-antibiotic strategies are effective for reducing the risk of infective complications in men undergoing prostate biopsy?

6.2   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 [44] 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 [45]. Infection is the most clinically significant harm experienced by men following prostate biopsy and includes urinary tract infection, prostatitis, and urosepsis. There is some evidence that the risk is increasing [46]. 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.

6.3   Diagnostic Evaluation
Urine culture prior to prostate biopsy has an uncertain predictive value [47].

6.4   Disease Management
The focus is on prevention of infectious complications. Possible strategies include antibiotic prophylaxis [48] for which the 2015 guideline should be consulted [13] and non-antibiotic strategies the effectiveness of which will be described in this section. Established infection is treated according to standard pathways [44].

6.5   Evidence summary
A systematic search of the literature to March 2015 identified 1,550 titles of which 133 were selected for full text review and 50 randomised-controlled trials (RCT) were included [49-99]. Infectious complications were generally measured as a secondary outcome.

6.5.1   Number of biopsy cores
Meta-analysis of seven trials involving 1,162 men found no evidence that extended biopsy (> 6-24 cores) templates resulted in more infectious complications than standard templates (6-12 cores) (LE 1a) [49-55].

6.5.2   Periprostatic injection of local anaesthetic
Meta-analysis of 23 RCTs with 3,397 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 [LE 1a] [56-78]. Five other RCTs investigated differing injection techniques with no difference found in infective complications [95-97, 99-100]. A pooled analysis could not be performed because of heterogeneous study designs.

6.5.3   Route of biopsy
Three RCTs involving 446 men compared transrectal and transperineal routes of biopsy [79-81]. 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 [LE 1b].

6.5.4   Rectal preparation
Meta-analysis of six trials including 1,446 men showed that use of a rectal povidone-iodine preparation before biopsy in addition to antibiotic prophylaxis resulted in a lower rate of infectious complications [RR (95% CIs) =0.53 (0.41 to 0.70)] [LE 1a] [82-87]. This was in agreement with a previous meta-analysis which included four of these trials [101]. Single RCTs showed no evidence of benefit for perineal skin disinfection [88] or use of phosphate or glycine rectal enema [89, 90].

6.5.5   Other interventions
Combining data from two RCTs with 253 participants showed that single biopsy use of biopsy needles resulted in nine infectious complications compared to 22 with single patient use of the biopsy needle. The difference was not significant [RR (95% CIs) = 0.51 (0.24 to 1.08)] [92, 93]. A single RCT found no evidence that disinfection of a single patient use needle between cores resulted in fewer infectious complications [94].

6.6   Recommendation on non-antibiotic strategies for reducing the risk of infective complications in men undergoing prostate biopsy

Recommendation	LE	GR
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy in addition to antibiotic prophylaxis if local risk of infectious complication is high.	1a	B*

*Downgraded as highest quality trial in meta-analysis showed no difference [81]

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8.   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

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**European
Association
of Urology**

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urolithiasis Guidelines Panel have prepared these guidelines to help urologists assess evidence-based management of stones/calculi and incorporate recommendations into clinical practice. The 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.

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 translated versions and scientific publications are available [1-6]. 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 2016 document presents a limited update of the 2015 publication of the EAU Urolithiasis Guidelines.

1.4.2 Summary of changes

Key changes for the 2016 publication:
The literature for the entire document has been assessed and updated, whenever relevant (see Methods section below).

- Limited changes were made to the Section 3.4.1.1 - Renal colic
- The findings of the systematic review performed by the Panel (What are the benefit and harms of URS compared with SWL in the treatment of upper ureteral stones in children and adults? [305]) have been included in Section 3.4.3.3 - Selection of procedure for active removal of ureteral stones.
- Section 3.4.1.3.2 - Antithrombotic therapy and stone treatment - has been expanded with new data. New table 3.4.1 - Risk stratification for bleeding and table 3.4.2 - Suggested therapies for antithrombotic therapy in stone removal have been added.
- Figure 3.4.1 - Treatment algorithm for renal calculi has been amended; priority of treatment modalities has changed to shockwave lithotripsy and ureterorenoscopy as first choice of treatment modalities for small upper urinary stones.
- Recent data has been included in Section 3.4.3.1.2 - Pharmacological treatment, Medical expulsive therapy (MET), which resulted in a lower recommendation (2015 recommendation was GR A).

Recommendation for MET	LE	GR
Offer α-blockers as MET as one of the treatment options.	1a	C

2.   METHODS

2.1   Data identification
For the 2016 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 during the period from August 11th 2014 to September 4th, 2015. Databases covered by the search included Medline, EMBASE and the Cochrane Libraries. A total of 487 unique records were identified, and screened for relevance. The search strategy is published online: http://uroweb.org/guideline/urolithiasis/?type=appendices-publications.

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:
*   What are the comparative benefits and harms of the different percutaneous nephrolithotomy (PCNL) tract sizes? [7].
*   What are the benefits and harms of ureteroscopy (URS) compared with shock wave lithotripsy (SWL) in the treatment of upper ureteral stones in children and adults? [305].

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   Review
The 2015 Urolithiasis Guidelines were subjected to peer review prior to publication.

2.3   Future goals
Further results on ongoing and new systematic reviews will be included in the 2017 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% [9]. 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 is reported [10] (Table 3.1.1).

Table 3.1.1: Prevalence and incidence of urolithiasis from two European countries [11, 12]

	Germany 2000 (%)	Spain 2007 (%)
Prevalence	4.7	5.06
Females	4.0	NA
Males	5.5	NA
Incidence	1.47	0.73
Females	0.63	NA
Males	0.84	NA

Stones can be classified into those caused by: infection, or non-infectious causes (infection and non-infection stones); genetic defects [13]; or adverse drug effects (drug stones) (Table 3.1.2).

Table 3.1.2: 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 3.1.3 lists the clinically most relevant substances and their mineral components.

Table 3.1.3: Stone composition

Chemical name	Mineral name	Chemical formula
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4.H_2O$
Calcium oxalate dihydrate	Wheddelite	$CaC_2O_4.2H_2O$
Basic calcium phosphate	Apatite	$Ca10(PO_4)_6.(OH)_2$
Calcium hydroxyl phosphate	Carbonite apatite	$Ca_5(PO_3)_3(OH)$
b-tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$
Calcium hydrogen phosphate	Brushite	$PO_4.2H_2O$
Calcium carbonate	Aragonite	$CaCO_3$
Octacalcium phosphate		$Ca_8H_2(PO_4)_6.5H_2O$
Uric acid	Uricite	$C_5H_4N_4O_3$
Uric acid dihydrate	Uricite	$C_5H_4O_3.2H_20$
Ammonium urate		$NH_4C_5H_3N_4O_3$
Sodium acid urate monohydrate		$NaC_5H_3N_4O_3.H_2O$
Magnesium ammonium phosphate	Struvite	$MgNH_4PO_4.6H_2O$
Magnesium acid phosphate trihydrate	Newberyite	$MgHPO_4.3H_2O$
Magnesium ammonium phosphate monohydrate	Dittmarite	$MgNH_4(PO_4).1H_2O$
Cystine		$[SCH_2CH(NH_2)COOH]_2$
Gypsum	Calcium sulphate dihydrate	$CaSO_4.2H_2O$
	Zinc phosphate tetrahydrate	$Zn_3(PO_4)2.4H_2O$
Xanthine		
2,8-Dihydroxyadenine		
Proteins		
Cholesterol		
Calcite		
Potassium urate		
Trimagnesium phosphate		

Melamine		
Matrix		
Drug stones	• 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 [11, 14]. 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 3.1.4) [15, 16].

Table 3.1.4: High-risk stone formers [15-25]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Brushite-containing stones (CaHPO4.2H$_2$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., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion) and bariatric surgery [21]
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
Drugs associated with stone formation
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

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 [11, 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 here.

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. US 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 radiography is 44-77% and 80-87%, respectively [32]. KUB radiography should not be performed if NCCT is considered [33], however, it is helpful in differentiating between radiolucent and radiopaque stones and 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 seems to be significantly more accurate than IVP [34].

Recommendation	LE	GR
Following initial US assessment, use NCCT to confirm stone diagnosis in patients with acute flank pain, because it is superior to IVU.	1a	A

IVU = intravenous urography; NCCT = non-contrast enhanced computed tomography; US = ultrasound.

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 (Table 3.1).

Radiation risk can be reduced by low-dose CT [39]. In patients with 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 [40]. A meta-analysis of prospective studies [41] 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).

Table 3.3.1: Radiation exposure of imaging modalities [42-45]

Method	Radiation exposure (mSv)
KUB radiography	0.5-1
IVU	1.3-3.5
Regular-dose NCCT	4.5-5
Low-dose NCCT	0.97-1.9
Enhanced CT	25-35

3.3.1.2   Radiological evaluation of patients with renal stones

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 CT in complex cases because it enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance. IVU may also be used.	4	C

*Upgraded based on panel consensus.
CT = computed tomography; IVU = intravenous urography.

*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 3.3.2: Recommendations: basic laboratory analysis - emergency urolithiasis patients
        [16, 17, 46, 47]

Recommendations	GR
Urine	
Dipstick test of spot urine sample	A*
• red cells	A
• white cells	
• nitrite	
• approximate urine pH	
Urine microscopy and/or culture	
Blood	
Serum blood sample	A*
• creatinine	
• uric acid	
• (ionised) calcium	
• sodium	
• potassium	
Blood cell count	
• CRP	
Perform a coagulation test (PTT and INR) if intervention is likely or planned.	A*

*Upgraded based on panel consensus.
CPR = C-reactive protein; INR = international normalised ratio; PTT = partial thromboplastin time.

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 [16]. Stone-specific metabolic evaluation is described in Chapter 4.

The easiest means to achieve correct diagnosis is by analysis of a passed stone using a validated method as listed below (see 3.2.2). Once mineral composition is known, a potential metabolic disorders 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 [48].

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) [49-51]. Equivalent results can be obtained by polarisation microscopy, but only in centres with expertise. Chemical analysis (wet chemistry) is generally deemed to be obsolete [49].

Recommendations	LE	GR
Perform stone analysis in first-time formers using a valid procedure (XRD or IRS).	2	A
Repeat stone analysis in patients: • presenting with reccurent 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 [47].	2	B

IRS = infrared spectroscopy; XRD = X-ray diffraction.

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 amount of radiation delivered. X-ray imaging during the first trimester should be reserved for patients in which alternative imaging methods have failed [52, 53].

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 [54].

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 [55, 56].

Low dose CT protocols reduce the radiation exposure and are currently recommended to be used judicially in pregnant women as a last-line option [57, 58].

Recommendations	LE	GR
Use ultrasound as the preferred method of imaging in pregnant women.	1a	A*
In pregnant women, use MRI as a second-line imaging modality.	3	C
In pregnant women, use low-dose CT as a last-line option.	3	C

*Upgraded following panel consensus.
CT = computed tomography; MRI = magnetic resonance imaging.

3.3.3.2   Children
Paediatric patients 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).

Summary of evidence	LE
In paediatric patients, the most common non-metabolic disorders facilitating stone formation are vesicoureteral reflux, ureteropelvic junction obstruction, neurogenic bladder, and other voiding difficulties [59].	4

Recommendations	GR
In all paediatric patients, complete a metabolic evaluation based on stone analysis.	A
Collect stone material for analysis to classify the stone type.	A*

Upgraded following panel consensus.

3.3.3.2.1 Diagnostic imaging

When selecting diagnostic procedures to identify urolithiasis in paediatric patients, it should be remembered that these patients might be uncooperative, require anaesthesia, or be sensitive to ionising radiation [60-62]. 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 [60] in paediatrics. 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 [63-67].

Colour Doppler US shows differences in the ureteric jet [64] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [65].

Nevertheless, US fails to identify stones in > 40% of paediatric patients [66-69] (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) [70]. 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 [45] [71].

In children, only 5% of stones escape detection by NCCT [57, 64, 71]. Sedation or anaesthesia is rarely needed with modern high-speed CT apparatus.

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 [72].

Recommendations	GR
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 US does not provide the required information, perform a KUB radiography (or low-dose NCCT).	B

US = ultrasound; KUB = kidney, ureter, bladder; NCCT = non-contrast enhanced computed tomography.

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 [73, 74].

Non-steroidal anti-inflammatory drugs (NSAIDs) including metamizole (synonym: dipyrone), a pyrazolone NSAID, are effective in patients with acute stone colic [75, 76], and have better analgesic efficacy than opioids. 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, 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 [77, 78].

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs, and carry a greater likelihood of further analgesia being needed [79, 80] (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 [80-82]. Although diclofenac can affect renal function in patients with already reduced function, it has no functional effect in patients with normal kidney function [83] (LE: 1b).

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 7 days of treatment [82]. Daily α-blockers might reduce recurrent colic (Section 3.4.3.1.2).

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 an NSAID as the first drug of choice. e.g. metamizol (dipyrone); alternatively, depending on cardio-vascular risk factors diclofenac*, indomethacin or ibuprofen**.	A
Offer hydromorphine, pentazocine or tramadol as a second choice.	C
Use α-blockers to reduce recurrent colic in informed patients.	C

Affects glomerular filtration rate (GFR) in patients with reduced renal function (LE: 2a).
**Recommended to counteract recurrent pain after ureteral colic.*
NSAID = nonsteroidal anti-inflammatory drug.

Summary of evidence	LE
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 [84, 85].

Only one RCT [86] assessed 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 [84]. Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy.

In children, ureteric stents might have some advantage compared to PCN in case of acute anuria [87].

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. Intensive care might become necessary.

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 risk of infection following ureteroscopy and percutaneous stone removal, no clear-cut evidence exists [88, 89]. 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 [90]. Single dose administration was found to be sufficient [91].

Recommendations	LE	GR
Exclude or treat UTIs prior to stone removal.	1b	A
Offer perioperative antibiotic prophylaxis to all patients undergoing endourological treatment.	1b	A*

UTI = urinary tract infection

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 and during stone removal [92-96]. In patients with an uncorrected bleeding diathesis, the following are at elevated risk of haemorrhage or perinephric haematoma (PNH) (high-risk procedures):
- shockwave lithotripsy (SWL) (hazard ratio of PNH up to 4.2 during anticoagulant/antiplatelet medication [97] [LE: 2]);
- percutaneous nephrolithotripsy;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [92, 98, 99].

Shockwave lithotripsy is feasible and safe after correction of the underlying coagulopathy [100-104]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, ureterorenoscopy (URS), in contrast to SWL and PNL, might offer an alternative approach since it is associated with less morbidity [105-

109]. Only data on flexible ureteroscopy is available which support the superiority of URS in the treatment of proximal ureteric stones [106, 110].

Table 3.4.1: Risk stratification for bleeding [94-96, 111]

Low-risk bleeding procedures	Cystoscopy Flexible cystoscopy Ureteral catheterization Extraction of ureteric stent Ureteroscopy
High-risk bleeding procedures	SWL Percutaneous nephrostomy Percutaneous nephrollithotripsy

Table 3.4.2: Suggested strategy for antithrombotic therapy in stone removal [94-96]
(In collaboration with cardiologist only)

	Bleeding risk	Risk of thromboembolism		
		Low risk	**Intermediate risk**	**High risk**
Warfarin Dabigatran Rivaroxaban Apixaban	Low-risk procedure	May be continued INR low therapeutic range 2.5.	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 possible.	Elective surgery: postpone. Non-deferrable surgery: continue.
Thienopyridine agents (P2Y12 receptor inhibitors)	Low-risk procedure	Discontinue 5 days before intervention. Resume within 24-72 hours with a loading dose.	Continue	Elective surgery: postpone. Non-deferrable surgery: continue.
	High-risk procedure	Discontinue 5 days before intervention and resume within 24-72 hours with a loading dose.	Elective surgery: postpone. Non-deferrable surgery: discontinue 5 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 5 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 caliceal stone.		C
Decide on temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, in consultation with the internist.	3	B
Prefer retrograde (flexible) ureterorenoscopy 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 anaesthesiological measurements, 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 in 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 HU in unenhanced CT. Stones with density > 1,000 HU on NCCT are less likely to be disintegrated by SWL.		
Attempt to dissolve radiolucent stones (See Section 3.4.2.1.2.2).	2a	B

CT = computed tomography; HU = Hounsfield unit; NCCT = non-contrast enhanced computed tomography; SWL = shockwave lithotripsy.

3.4.1.3.5 Steinstrasse

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter, which does not pass within a reasonable period of time, and interferes with the passage of urine [112]. Steinstrasse occurs in 4-7% cases of SWL [113], and the major factor in steinstrasse formation is stone size [114].

Insertion of a ureteral stent before SWL prevents formation of steinstrasse in stones > 15 mm in diameter [115]. A major problem of steinstrasse is ureter obstruction, which can be silent in 23% of cases [116, 117].

When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy significantly increases stone expulsion and reduces the need for endoscopic intervention [118, 119].

Summary of evidence	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse [118].	1b
When spontaneous passage is unlikely, further treatment of steinstrasse is indicated.	4
Shockwave lithotripsy is indicated in asymptomatic and symptomatic cases, with no evidence of UTI, when large stone fragments are present [120].	4
Ureteroscopy is effective for the treatment of steinstrasse [121].	3
Placement of a percutaneous nephrostomy tube or ureteral stent is indicated for symptomatic ureteric obstruction with/without UTI.	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 shockwave 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 observation, 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).

Summary of evidence	LE
It is still debatable whether renal stones should be treated, or whether annual follow-up is sufficient for asymptomatic caliceal stones that have remained stable for 6 months.	

Recommendations	GR
Follow-up periodically in cases where renal stones are not treated (initially after 6 months and yearly follow-up of symptoms and stone status [US, KUB or CT]).	A*

Upgraded based on panel consensus.
CT = computed typography; KUB = kidney, bladder, ureter (plan film); US = ultrasound.

3.4.2.1.2   Pharmacological treatment
3.4.2.1.2.1 Percutaneous irrigation chemolysis
Today, percutaneous chemolysis is rarely used. Percutaneous irrigation chemolysis may be an option
for infection- and uric acid stones [122, 123]. For dissolution of struvite stones, Suby's G solution (10%
hemiacidrin; pH 3.5-4) can be used [124].

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 may provide information on the type of stone.
        Oral chemolitholysis is based on alkalinisation of urine by application of alkaline citrate or sodium
bicarbonate [123, 125]. The pH should be adjusted to 7.0-7.2. Chemolysis is more effective at a higher pH,
which might lead to 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 [126]. A combination of alkalinisation with tamsulosin seems to achieve the
highest stone-free rates (SFRs) for distal ureteral stones [126].

Recommendations	GR
Inform the patient how to modify the dosage of alkalising 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 has an important influence on retreatment rate and final outcome of SWL.

3.4.2.1.3.1 Contraindications of extracorporeal SWL
There are several contraindications to the use of extracorporeal SWL, including:
•   pregnancy, due to the potential effects on the foetus [127];
•   bleeding diatheses, which should be compensated for at least 24 h before and 48 h after treatment [128];
•   uncontrolled UTIs;
•   severe skeletal malformations and severe obesity, which prevent targeting of the stone;
•   arterial aneurysm in the vicinity of the stone [129];
•   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 SFR [130] (LE: 1b). A JJ stent reduces the risk of renal colic and obstruction, but does not reduce formation of steinstrasse or infective complications [131].

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 [132].

Shock wave rate
Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFR [83, 133-137]. Tissue damage increases with shock wave frequency [138-142].

Recommendation	LE	GR
Use a shock wave frequency of 1.0-1.5 Hz.	1a	A

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 [140], which prevents renal injury [143, 144]. Animal studies [145] and a prospective randomised study [146] 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 [147].
        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
Clinical experience has shown that repeat sessions are feasible (within 1 day for ureteral stones).	4

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 reflect 99% of shock waves [148]. Ultrasound gel is probably the most widely used agent available for use as a lithotripsy coupling agent [149].

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 [150].

Recommendation	LE	GR
Maintain careful fluoroscopic and/or ultrasonographic monitoring during the procedure.		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 [151-153].

Recommendation	LE	GR
Use proper analgesia because it improves treatment results by limiting 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) [154-156].

Recommendation	LE	GR
In the case of infected stones or bacteriuria, prescribe antibiotics prior to SWL.	4	C

Medical therapy after extracorporeal shock wave lithotripsy
Medical expulsion therapy after SWL for ureteral or renal stones can expedite expulsion and increase SFRs, as well as reduce additional analgesic requirements [157-166] (Section 3.4.2.1.2.1.2).

3.4.2.1.3.3 Complications of extracorporeal shock wave lithotripsy
Compared to PNL and URS, there are fewer overall complications with SWL [167, 168] (Table 3.4.1).

Table 3.4.1: SWL-related complications [113, 116, 169-181]

Complications			%	Ref.
Related to stone fragments	Steinstrasse		4 - 7	[113, 116, 169]
	Regrowth of residual fragments		21 - 59	[170, 171]
	Renal colic		2 - 4	[172]
Infectious	Bacteriuria in non-infection stones		7.7 - 23	[170, 173]
	Sepsis		1 - 2.7	[170, 173]
Tissue effect	Renal	Haematoma, symptomatic	< 1	[174]
		Haematoma, asymptomatic	4 - 19	[174]
	Cardiovascular	Dysrhythmia	11 - 59	[170, 175]
		Morbid cardiac events	Case reports	[170, 175]
	Gastrointestinal	Bowel perforation	Case reports	[176-178]
		Liver, spleen haematoma	Case reports	[178-181]

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 [6, 182-186].

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 [187]. 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 intrarenal pelvic pressure [7] [188-192].

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 [105].

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 (the 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 [193]. Flexible endoscopes require laser lithotripsy to maintain tip deflection and the Ho:YAG laser
has become the standard, as for ureteroscopy [194]. Electrohydraulic lithotripsy (EHL) is highly effective, but is
no longer considered as a first-line technique, due to possible collateral damage [195].

Recommendations	GR
Use ultrasonic, ballistic and Ho:YAG devices for intracorporeal lithotripsy during PNL.	A*
When using flexible instruments, use the Ho:YAG laser since it is currently the most effective device.	

*Upgraded based on panel consensus.
Ho:YAG = holmium:yttrium-aluminium-garnet; PNL = percutaneous nephrolithotomy.

Preoperative imaging
Preprocedural 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) [196].

Recommendation	GR
Perform preprocedural 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.

Antibiotic therapy - see General recommendations and precautions for stone removal (See 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 OR time. In some series, stone-free rate 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 [197-199]. The Urolithiasis Guidelines Panel will be setting up a
systematic review to assess this topic.

Puncture
Colon interposition in the access tract of PNL can lead to colon injuries. Pre-operative CT or intraoperative US
allows identification of the tissue between the skin and kidney and lowers the incidence of bowel injury [200,
201].

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 [200].

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 intraoperative 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 [202, 203].

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 [204-206].

Recommendation	LE	GR
In uncomplicated cases, perform a tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) PNL procedures as it is a safe alternative.	1b	A

PNL = percutaneous nephrolithotomy.

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 PNL [207]

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 [208, 209]. Intraoperative irrigation pressure < 30 mm Hg 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. Superselective 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 [210-212]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [211-213]. 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 [214].

Recommendation	GR
Use flexible URS in case PNL or SWL are not an option (even for stones larger than 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

PNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy; URS = ureterorenoscopy.

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 [215-221]. 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 [222-229].

Recommendations	LE	GR
Offer laparoscopic or open surgical stone removal in rare cases in which SWL, (flexible) URS and PNL 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

PNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy; URS = ureterorenoscopy.

3.4.2.2   Indication for active stone removal of renal stones [230]
- 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 5-year event probability of 48.5% [231-234]. A prospective RCT with > 2 years clinical follow-up reported no significant difference between SWL and observation when they compared asymptomatic caliceal stones < 15 mm in terms of SFR, symptoms, requirement for additional treatment, quality of life (QoL), renal function, or hospital admission [235]. Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported [231, 233, 236]. In a follow-up period of almost 5 years after SWL, two series have demonstrated that up to 25% of patients with small residual fragments needed treatment [171, 237].

Summary of evidence	LE
Although the question of whether caliceal stones should be treated is still unanswered, stone growth, de novo obstruction, associated infection, and acute and/or chronic pain are indications for treatment [230, 238, 239].	3

Recommendations	GR
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
Shockwave 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 [240-243]. Shockwave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [242, 244]. 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 has the risk of ureteral obstruction (colic or steinstrasse) with the need for adjunctive procedures (Figure 3.4.1) [167]. Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm in uncomplicated cases as SFR is decreasing, and staged procedures have become necessary [245-247]. 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 intrarenal 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 [167, 240-244, 247-254].

The following can impair successful stone treatment by SWL:
- steep infundibular-pelvic angle;
- long calyx;
- narrow infundibulum (Table 3.4.4) [140, 250].

Further anatomical parameters cannot yet be established. The value of supportive measures such as inversion, vibration or hydration remains under discussion.

Table 3.4.4: Unfavourable factors for SWL success for lower caliceal stones [140, 250, 251, 255]

Factors that make SWL less likely
Shockwave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).
Steep infundibular-pelvic angle.
Long lower pole calyx (> 10 mm).
Narrow infundibulum (< 5 mm).

If there are negative predictors for SWL, PNL and RIRS might be a reasonable alternative, even for smaller calculi [248]. Retrograde renal surgery seems to have comparable efficacy to SWL [167, 244]. Recent clinical experience has suggested a higher stone free rate 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 [250, 256-258]. 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 SWL and endourology (PNL, 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 URS or SWL. However, in that case 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

PNL = percutaneous nephrolithotomy; RIRS = retrograde renal surgery; SWL = shock wave lithotripsy; URS = ureterorenoscopy.

Figure 3.4.1: Treatment algorithm for renal calculi
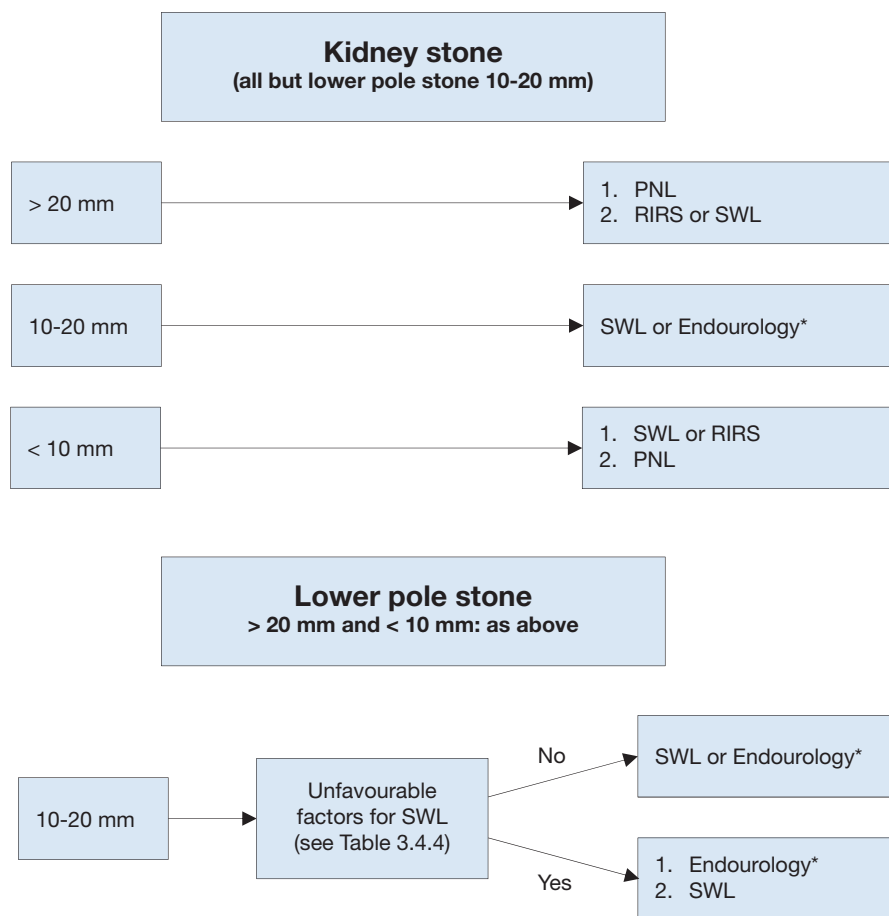
The term 'Endourology' encompasses all PNL and URS interventions.
PNL = percutaneous nephrolithotomy; RIRS = retrograde renal surgery; SFR = stone-free rate; SWL = shockwave lithotripsy; URS = ureterorenoscopy;

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 [259]. It is estimated that 95% of stones up to 4 mm pass within 40 days [6].

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), observation with periodic evaluation is an optional initial treatment.	1a	A
Appropriate medical therapy should be offered to these patients to facilitate stone passage during observation.		

See stratification data [6].

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 [6]. Therefore, the Panel decided not to include stone size in this recommendation and would rather limit "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 (MET)
Medical expulsive therapy should only be used in informed patients. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). When using α-blockers for

MET possible side-effects include retrograde ejaculation and hypotension [82].

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 [82, 261].

Meta-analyses based on small, single centre trials should be interpreted on principle with caution even if the pooled effect is statistically significant. With these limitations in mind, MET has been recommended by the EAU Urolithiasis Guidelines Panel. Further large, multicentric RCTs are needed to confirm the present evidence. The recently published data from Pickard *et al.* is based on a methodologically high quality trial with robust concealment of allocated treatment, demonstrating that tamsulosin and nifedipine are not effective in the routine expectant management of ureteral stones causing a ureteric colic [262]. Although not primarily investigated, this study seriously questions the effectiveness of MET using α- or calcium channel blockers; not only for ureteral stones and generated fragments but also for their capability of limiting pain.

Summary of evidence	LE
There is evidence in a large number of small single centre trials that MET accelerates spontaneous passage of ureteral stones and fragments generated with SWL, and limits pain [82, 119, 166, 261, 263-267].	1a
There is new evidence from a large multicentric high quality trial that tamsulosin and nifedipine have no expulsive effect, nor limit pain in patients with ureteral stones.	1b

Based on studies with a limited number of patients [268, 269] (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. Insufficient data exist to support the use of corticosteroids in combination with α-blockers as an accelerating adjunct [268-270].	1b
Patients who elect for an attempt at spontaneous passage or MET should have well-controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve.	

Recommendations for MET	LE	GR
Offer α-blockers as MET as one of the treatment options.	1a	C
Counsel patients regarding the lack of efficacy in a recent large multicentric trial, attendant risks of MET, including associated drug side effects as well as inform the patient that α-blockers are administered off-label[†**].	1b	A*
Follow up patients in short intervals to monitor stone position and assessed 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.
MET = medical expulsion therapy.

3.4.3.1.2.1 Medical expulsive therapy after extracorporeal shock wave lithotripsy (SWL)
An RCT and a meta-analysis have shown that MET after SWL for ureteral or renal stones can expedite expulsion and increase SFRs and reduce analgesic requirements [163, 166, 262] (LE: 1a).

3.4.3.1.2.2 Medical expulsive therapy after ureteroscopy
Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes [271] (LE: 1b).

3.4.3.1.2.3 Medical expulsive therapy and ureteral stents (see 3.4.3.1.4.1.2)

3.4.3.1.2.4 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   SWL
For best clinical practice, see Section 3.4.2.1.4.1.2 (Renal stones).

Stenting
The 2007 AUA/EAU Guidelines on the management of ureteral calculi state that routine stenting is not recommended as part of SWL [6]. When the stent is inserted, patients often suffer from frequency, dysuria, urgency, and suprapubic pain [272].

Recommendation	LE	GR
Do no routinely use a stent as part of SWL treatment of ureteral stones.	1b	A

SWL = shock wave lithotripsy.

3.4.3.1.4 Endourology techniques
3.4.3.1.4.1 Ureteroscopy (URS)
The current standard for rigid ureterorenoscopes are tip diameters of < 8 F. Rigid URS can be used for the whole ureter [6]. However, technical improvements, enhanced quality and tools as well as the availability of digital scopes also favour the use of flexible ureteroscopes in the ureter [210].

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 [273].

Antegrade URS is an option for large, impacted proximal ureteral calculi [274] (Section 3.4.3.1.4.2).

Safety aspects
Fluoroscopic equipment must be available in the operating room. We recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [275, 276].

Balloon and plastic dilators should be available if necessary.
Prior rigid ureteroscopy 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 7-14 days offers an alternative procedure.

Recommendation	GR
Place a safety wire.	C

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 intrarenal pressure, and potentially reduces operating time [277, 278].

The insertion of ureteral access sheaths may lead to ureteral damage, whereas the risk was lowest in pre-stented systems [279]. No data on long-term consequences are available [279, 280]. 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 [281].

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 has become the gold standard for ureteroscopy and flexible nephroscopy (Section 3.4.2.1.4.1.2), because it is effective for all stone types [282, 283]. Pneumatic and US systems can be used with high disintegration efficacy in rigid URS [284, 285].

However, stone migration into the kidney is a common problem, which can be prevented by placement of special antimigration tools proximal of the stone [286].

Recommendation	LE	GR
Use Ho:YAG laser lithotripsy for (flexible) URS.	3	B

Ho:YAG = holmium:yttrium-aluminium-garnet; URS = ureterorenoscopy.

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 complications [287].

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 [288-290]. A ureteric catheter with a shorter indwelling time (1 day) may also be used, with similar results [291].

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 [292, 293]. A recently published meta-analysis provides evidence for improvement of ureteral stent tolerability with tamsulosin [294].

Summary of evidence	LE
In uncomplicated URS, a stent need not be inserted.	1a
An α-blocker can reduce stent-related symptoms.	1b

URS = ureterorenoscopy.

3.4.3.1.4.1.3 Complications
The overall complication rate after URS is 9-25% [6, 295, 296]. 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 ureteroscopy
Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i.e. large, impacted proximal ureteral calculi with dilated renal collecting system [297], or when the ureter is not amenable to retrograde manipulation [274, 298-301].

Recommendation	GR
Use percutaneous antegrade removal of ureteral stones as an alternative when SWL is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS.	A

SWL = shock wave lithotripsy; URS = ureterorenoscopy.

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; therefore, the reported data could not be used to compare procedures with each other or with SWL or URS. These more invasive procedures have yielded high SFRs [224].

Recommendation	LE	GR
For ureterolithotomy, perform laparoscopy for large impacted stones when endoscopic lithotripsy or SWL has failed.	2	B

SWL = shock wave lithotripsy.

3.4.3.2   Indications for active removal of ureteral stones [6, 259, 302]
Indications for active removal of ureteral stones are:
*   Stones with 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 a severe obesity, URS is a more promising therapeutic option than SWL.	2b

SWL = shockwave lithotripsy; URS = ureterorenoscopy.

3.4.3.2.5.1 Bleeding disorder
URS can be performed in patients with bleeding disorders, with a moderate increase in complications (see also Section 3.4.1.3) [105, 108].

3.4.3.3   Selection of procedure for active removal of ureteral stones
Overall SFRs after URS or ESWL 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 ureteroscopy have been significantly reduced [303, 304].
These findings are confirmed by the preliminary results of a recent systematic review performed by the Urolithiasis Guidelines Panel [305]. Compared to SWL, ureteroscopic management of proximal ureteral calculi is associated with significantly higher SFRs, lower re-treatment rates and less need for secondary and adjunctive procedures. However, ureteroscopic management is associated with higher complication rates and a longer hospital stay. Further well-designed RCTs with sufficient power are needed to better address the efficacy, complications and other treatment-related parameters of both modalities.

Figure 3.4.2: Recommended treatment options (if indicated for active stone removal) (GR: A*)
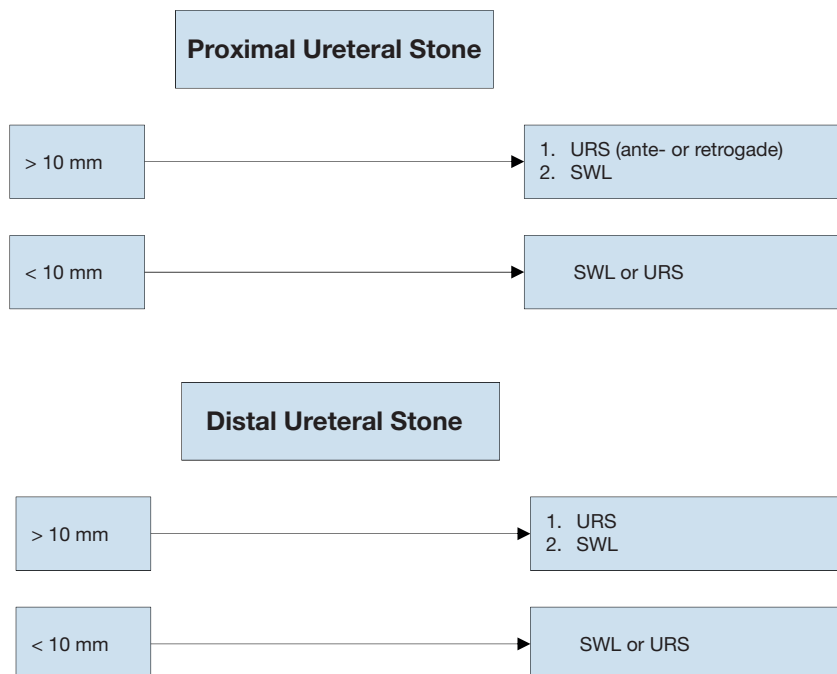
Upgraded following panel consensus.
SWL = shockwave lithotripsy; URS = ureterorenoscopy.

Recommendation	GR
Inform patients that 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 SWL.	A*

Upgraded following panel consensus.
SWL = shockwave lithotripsy; URS = ureteronoscopy.

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 [171, 306, 307].

Recommendations	LE	GR
Identify biochemical risk factors and appropriate stone prevention in patients with residual fragments or stones [171, 307, 308].	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 [308]. For all stone compositions, 21-59% of patients with residual stones required treatment within 5 years. Fragments > 5 mm are more likely than smaller ones to require intervention [171, 306, 309].

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 [310].

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 [311-313].

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 [314].	1b

Recommendations	LE	GR
After SWL and URS, and in the presence of residual fragments, offer MET using an α-blocker to improve fragment clearance.	1a	A

MET = medical expulsive therapy; SWL = shockwave lithotripsy; URS = ureteronoscopy.

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 [315-317]. 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 [318-320]. Although feasible, retrograde endoscopic and percutaneous removal of renal stones during pregnancy remain an individual decision and should be performed only in experienced centres [321].

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 are readily available primary options.	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 non-complicated 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 [322-324]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [325] (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 5 years [326].

3.4.5.2.2   Management
Smaller upper-tract stones can be treated effectively with SWL [299, 327]. In the majority, endourological techniques are necessary to achieve stone-free status [298]. 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 URS is the alternative.	4

Recommendation	GR
Perform PNL 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 SWL.	A*

PNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy; URS = ureterorenoscopy.

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. Transstomal manipulations in continent urinary diversion must be performed carefully to avoid disturbance of the continence mechanism [328].

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 [329], and if present, an open surgical approach should be considered.

3.4.5.2.3   Prevention
Recurrence risk is high in these patients [326]. Metabolic evaluation and close follow-up of the patients 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 [330].

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, vesicoureteral reflux, renal scarring, lower urinary tract reconstruction, and thoracic spinal defect [331]. The main issues 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 [332, 333].

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 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 [334]. 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 [335]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [330].

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.
- Hyperfiltration, excessively alkaline urine, renal tubular acidosis, and increased serum calcium caused by persistent tertiary hyperparathyroidism [336] are biochemical risk factors.
Stones in kidney allografts have an incidence of 0.2-1.7% [337-339].

Recommendation	LE	GR
Perform US or NCCT to rule out calculi in patients with transplanted kidneys, unexplained fever, or unexplained failure to thrive (particularly in children) [340].	4	B

NCCT = non-contrast enhanced computed tomography; US = ultrasound.

3.4.5.4.2   Management
Treatment decisions for selecting the appropriate technique for stone removal from a transplanted kidney are difficult. Although management principles are similar to those applied in other single renal units [341-344], 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 ureteroscopy a valid treatment option for transplant calculi. However, one must be aware of potential injury to adjacent organs [345-347]. Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [348-350].

Summary of evidence	LE
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.	
SWL for small calyceal stones is an option with minimal complication risk, but localisation of the stone can be challenging and SFRs are poor [351, 352].	4

Recommendations	GR
Offer patients with transplanted kidneys, any of the contemporary treatment modalities, including shockwave therapy, (flexible) ureteroscopy, and percutaneous nephrolithotomy as management options.	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

Caliceal diverticulum stones	• SWL, PNL (if possible) or RIRS. • Can also be removed using laparoscopic retroperitoneal surgery [353-357]. • Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due to narrow caliceal neck.
Horseshoe kidneys	• Can be treated in line with the options described above [358]. • Passage of fragments after SWL might be poor. • Acceptable stone free rates can be achieved with flexible ureteroscopy [359].
Stones in pelvic kidneys	• SWL, RIRS, PNL or laparoscopic surgery. • For obese patients, the options are RIRS, PNL or open surgery.
Stones formed in a continent reservoir	• See Section 3.4.4. • Each stone must be considered and treated individually.
Patients with obstruction of the ureteropelvic junction	• When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. • URS together with endopyelotomy with Ho:YAG. • Incision with an Acucise balloon catheter might be considered, provided the stones can be prevented from falling into the pelvi-ureteral incision [360-363].

Ho:YAG = holmium:yttrium-aluminium-garnet; SWL = shockwave lithotripsy; PNL = percutaneous nephrolithotomy; URS = ureterorenoscopy; RIRS = retrograde renal surgery.

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 [11, 364, 365]. 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 [366-369].
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 [49]. For endourological procedures, the smaller organs in children must be considered when selecting instruments for PNL or URS. Anticipation of the expected 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 [59].	4

3.4.6.1.1   Medical expulsive therapy (MET) 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 few data to demonstrate their safety and efficacy in children; however tamsulosin seems to support stone passage [62, 370-372].

3.4.6.1.2 Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy remains the least-invasive procedure for stone management in children [373-378].

SFRs 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 [375, 379]. As in adults the slow delivery rate of shock waves may improve the stone clearance rates [379]. Stones located in calices, as well as 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% [375, 377].

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 avoid patient and stone motion and the need for repositioning [375, 377]. With modern lithotripters, intravenous sedation or patient-controlled analgesia have been used in selected cooperative older children [380] (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 [381-384].

If the stone burden requires an 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 [373-375].

Summary of evidence	LE
In children, the indications for SWL are similar to those in adults; however, they pass fragments more easily.	3
Children with renal stones of a diameter up to 20 mm (~300 mm^2) are ideal candidates for SWL.	1b

SWL = shockwave lithotripsy.

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 nephrolithotripsy (PNL)

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 [385-389]. 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 [385].

As for adults, tubeless PNL is safe in children, in well-selected cases [390, 391].

Summary of evidence	LE
For paediatric patients, the indications for PNL are similar to those in adults.	1a

Recommendation	GR
In children, perform PNL for the treatment of renal pelvic or caliceal stones with a diameter > 20 mm (~300 mm^2).	C

PNL = percutaneous nephrolithotomy.

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, calcium oxalate monohydrate or cystine stones, or stones in children with unfavourable anatomy and in whom localisation is difficult [392, 393].

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 [392-396].

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, are all safe and effective (Section 3.4.3.1.4.1.2) [397, 398].

Recommendation	LE	GR
For intracorporeal lithotripsy, use the same devices as in adults (Ho:YAG laser, pneumatic- and US lithotripters).	3	C

Ho:YAG = holmium:yttrium-aluminium-garnet; US = ultrasound.

Flexible ureteroscopy has become an efficacious treatment for paediatric upper urinary tract stones. It might be particularly effective for treatment of proximal ureteral calculi and for stones < 1.5 cm in the lower pole calices [398-401].

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 procedure has dropped significantly [402-404]. 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 [373, 374, 386]. Open surgery can be replaced by laparoscopic procedures in experienced hands [403, 404].

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 [405]. 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 [62, 406] (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
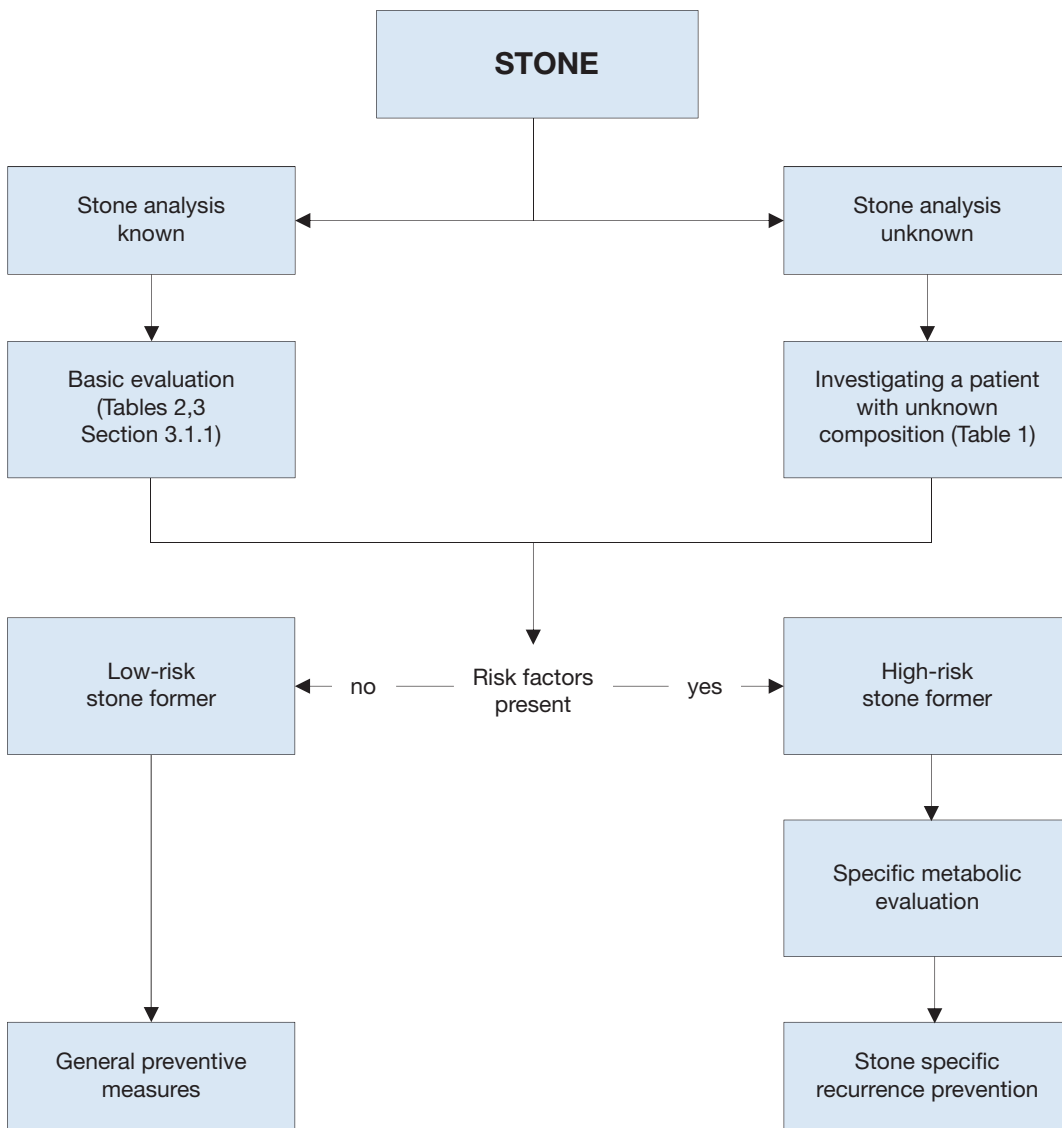
Only high-risk stone formers require specific metabolic evaluation. Stone type is the deciding factor for further diagnostic tests. The different stone types include:
- calcium oxalate;
- calcium phosphate;
- uric acid;
- ammonium urate;
- struvite (and infection stones);
- cystine;
- xanthine;
- 2,8-Dihydroxyadenine;
- drug stones;
- stones of unknown composition.

4.1.2   Urine sampling
Specific metabolic evaluation requires collection of two consecutive 24-h urine samples [407, 408]. The collecting bottles should be prepared with 5% thymol in isopropanol or stored at ≤ 8°C during collection to prevent the risk of spontaneous crystallisation in the urine [409, 410]. 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 [17, 409] using sensitive pH-dipsticks or a pH-meter.

Spot urine samples are an alternative method of sampling, particularly when 24-h urine collection is difficult, for example, in non-toilet trained children [411]. Spot urine studies normally link the excretion rates to creatinine [411], 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 20 days [412].

Follow-up studies are necessary in patients taking medication for recurrence prevention [413]. The first follow-up 24-h urine measurement is suggested 8-12 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-h urine measurements if necessary. Once urinary parameters have been normalised, it is sufficient to perform 24-h urine evaluation every 12 months. The panel realise that on this issue there is only very limited published evidence. The Urolithiasis Guidelines Panel aim to set up a systematic review 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 [414]

Blood parameter	Reference range	
Creatinine	20-100 µmol/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 µmol/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 [415-418]. 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 RTA)
	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

RTA = renal tubular acidosis.

Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in adults [419]

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-h urine samples in children [419]**

Calcium/24 h	Citrate/24 h		Cystine/24 h		Oxalate/24 h	Urate/24 h		
All age groups	Boys	Girls	< 10 y	> 10 y	All age groups	< 1 y	1-5 y	> 5 y
< 0.1 mmol/kg/ 24 h	> 1.9 mmol/ 1.73 m²/24 h	> 1.6 mmol/ 1.73 m²/24 h	< 55 µmol/ 1.73 m²/24 h	< 200 µmol/ 1.73 m²/24 h	< 0.5 mmol/ 1.73 m²/24 h	< 70 µmol/ kg/24 h	< 65 mµmol/ kg/24 h	< 55 µmol/ kg/24 h
< 4 mg/kg/24 h	> 365 mg/ 1.73 m²/24 h	> 310 mg/ 1.73 m²/24 h	< 13 mg/ 1.73 m²/24 h	< 48 mg/ 1.73 m²/24 h	< 45 mg / 1.73 m²/24 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 and 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 [420-422]. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [423]. If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased [424, 425]. One large fair-quality RCT randomly assigned men with more than one past renal stone of any type and soft drink consumption greater than 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 [422, 426].

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 [422, 427, 428].

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 [429-432]. 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 [423], 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 [433]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: should not be taken in excess [434, 435] 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 [430, 436]. The daily requirement for calcium is 1,000 to 1,200 mg [17]. Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate [422, 435, 437].

Sodium: the daily sodium (NaCl) intake should not exceed 3-5 g [17]. 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 [434, 435]. A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women [436, 438]. 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 [439, 440] and uric acid stones. Intake should not exceed 500 mg/day [17].

4.2.3   ***Lifestyle***
Lifestyle factors may influence the risk of stone formation, for example, obesity [441] and arterial hypertension [442, 443].

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-h urine volume ≥ 2.5 L.	1b	A
In patients with a small urine volume, advise patients to increase 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	[47, 422, 444-450]
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	[451-455]
Calcium	Enteric hyperoxaluria	1,000 mg/d	Intake 30 min before meals	Calcium oxalate	[435-437]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects	Cystine	[456, 457]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation	Calcium oxalate Uric acid	[458, 459]
l-Methionine	Acidification	600-1,500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[47, 460, 461]

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	[462, 463] low evidence
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d		Calcium oxalate Uric acid, Cystine	[464]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	[465]
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	[47, 462, 466-474]
Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 250 mg/d Max. 2,000 mg/d	Risk for tachyphylaxis and proteinuria.	Cystine	[475-478]

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 [47, 422, 445-447, 451-453, 458, 462-464, 466-473, 479-483].

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 [479].
- 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 $\leq$ 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 m^2/day in children) confirms hyperoxaluria.
  - primary hyperoxaluria (oxalate excretion mostly $\geq$ 1 mmol/day), appears in three genetically determined forms;

- o osecondary hyperoxaluria (oxalate excretion ≥ 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
- o omild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesuria (< 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
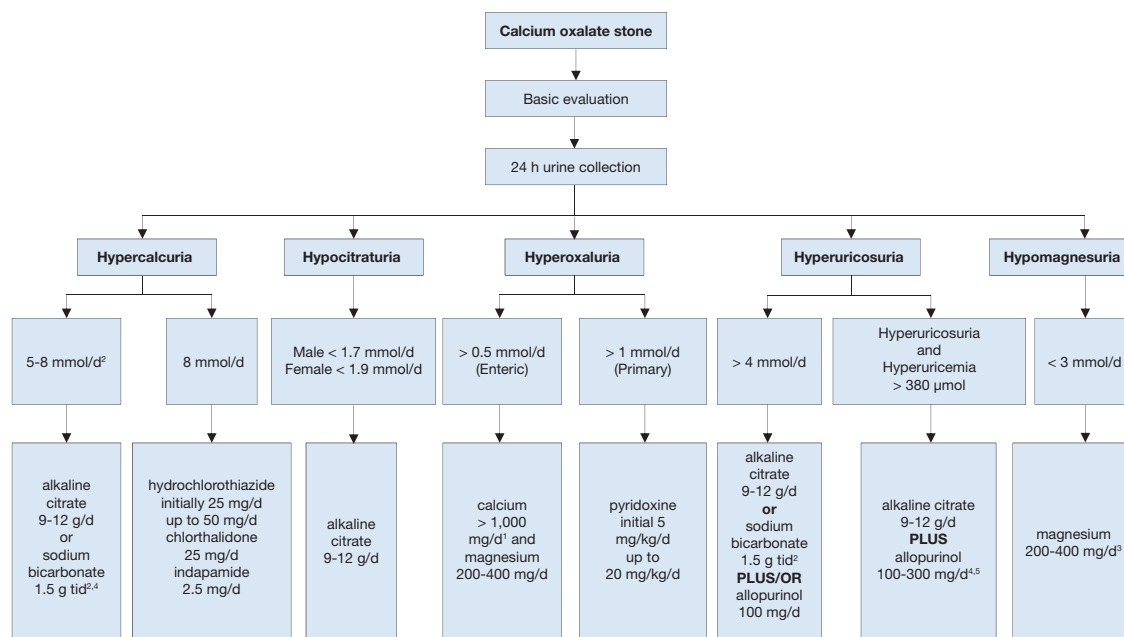
^{1} *Be aware of excess calcium excretion.*
^{2} *tid = three times/day (24h).*
^{3} *No magnesium therapy for patients with renal insufficiency.*
^{4} *There is no evidence that combination therapy (thiazide + citrate) (thiazide + allopurinol) is superior to thiazide therapy alone [466, 473].*
^{5} *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 [47, 422, 445-447, 451-453, 458, 462-464, 466-473, 479-483]. 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 [422].

4.4.4 *Recommendations for pharmacological treatment of patients with specific abnormalities in urine composition*

Urinary risk factor	Suggested treatment	LE	GR
Hypercalciuria	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 given 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
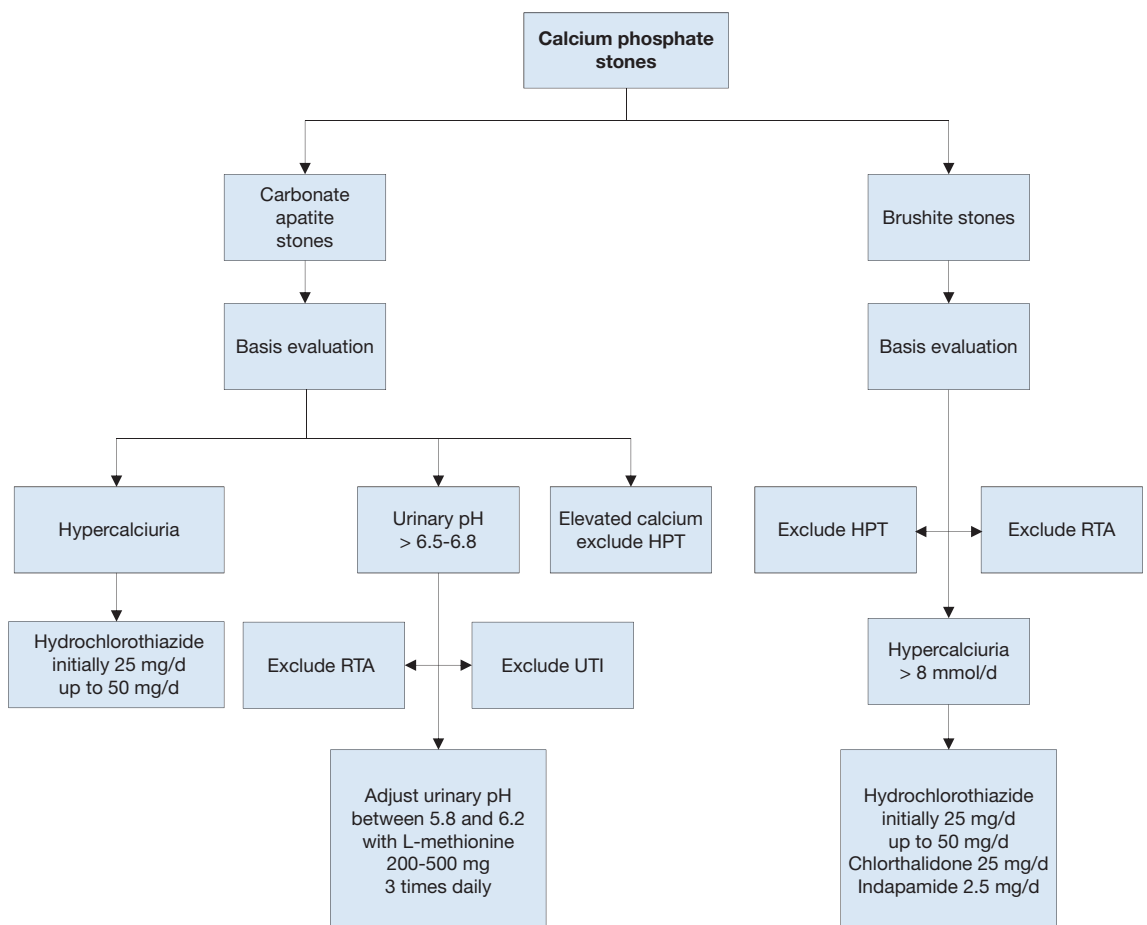
HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection.

4.5.3 *Pharmacological therapy [47, 422, 466, 467, 471, 483]*

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 helpful, 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 UTI.	3-4	C

UTI = urinary tract infection.

4.6 Disorders and diseases related to calcium stones

4.6.1 *Hyperparathyroidism [484-487]*

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 [487]*

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 [465]*

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/m^2 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 [437, 488]*

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 [437, 488];
• Sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
• Alkaline citrates to raise urinary pH and citrate.

Urinary risk factors and suggested management of enteric hyperoxaluria	LE	GR
Prescribe potassium citrate.	4	C
Advice patients to take a calcium supplement.	2	B
Advise patients to follow a diet reduced in fat and oxalate.	3	B

4.6.5 **Renal tubular acidosis** *[489, 490]*
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

Urinary pH
constantly > 5.8

↓

RTA Type I
possible

↓

Ammonium chloride
loading test**
(NH_4Cl 0.1 g/kg body weight)
Except for patients with
clinically confirmed
metabolic acidosis

Urine pH < 5.4
RTA excluded!

Urine pH > 5.4
RTA

Normal bicarbonate
in BGA
RTA - **incomplete**

Low bicarbonate in
BGA
RTA - **complete**
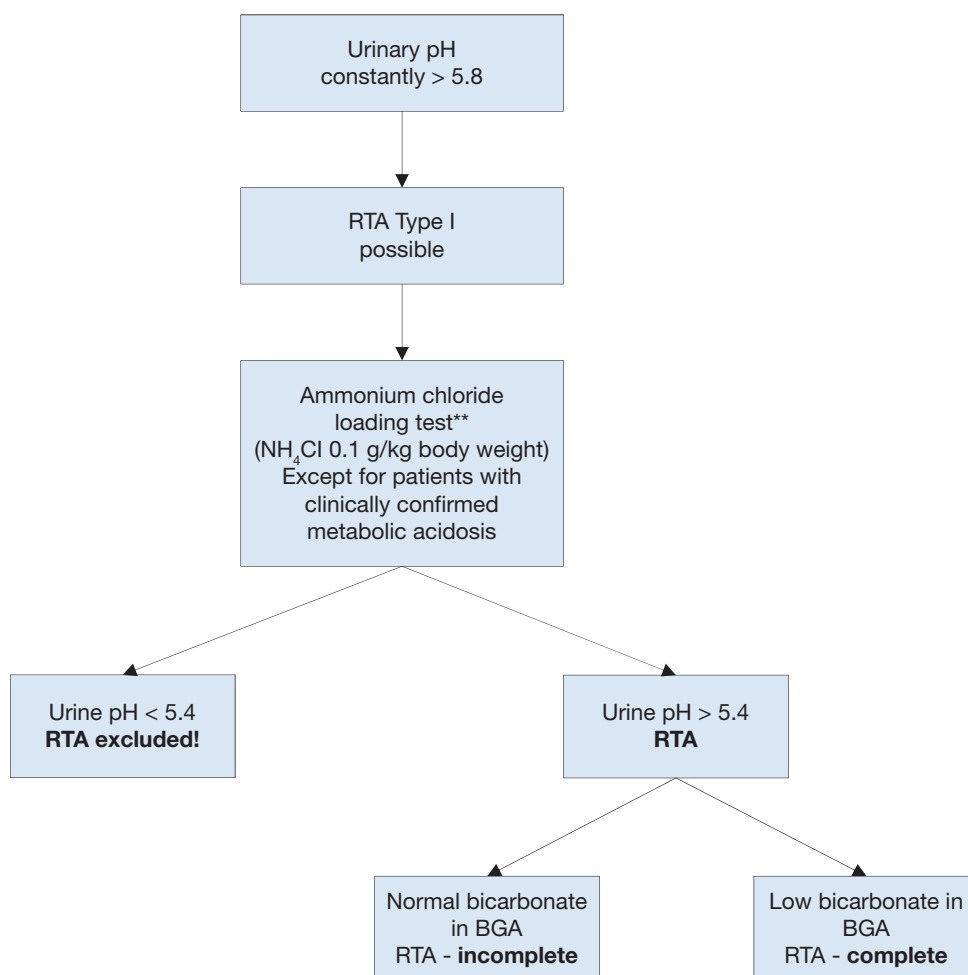
** An alternative Ammonium Chloride loading test using NH_4Cl load with 0.05 g/kg body weight over 3 days might provide similar results and may be better tolerated by the patient. A second alternative in these cases could be the furosemide acidification test.

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 hypercalciuria, primary parathyroidism, and 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 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 3 doses OR Sodium bicarbonate, 1.5 g, 3 times daily

Urinary risk factor and suggested management of renal tubular acidosis	LE	GR
Prescribe potassium citrate for distal RTA.	2b	B
Prescribe thiazide + potassium citrate for hypercalciuria.	1a	A

RTA = renal tubular acidosis.

4.6.6 *Nephrocalcinosis* [419]
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 4 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 [17]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [491]. 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 [492]. 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) [492].

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, hypokalemia 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 [493, 494]. Ammonium urate crystals form in urine at pH > 6.5, at high uric acid concentration when ammonium is present to serve as a cation [495-497].

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 [17, 411, 491-503]. 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 [504].

Figure 4.5: Diagnostic and therapeutic algorithm for uric acid- and ammonium urate stones
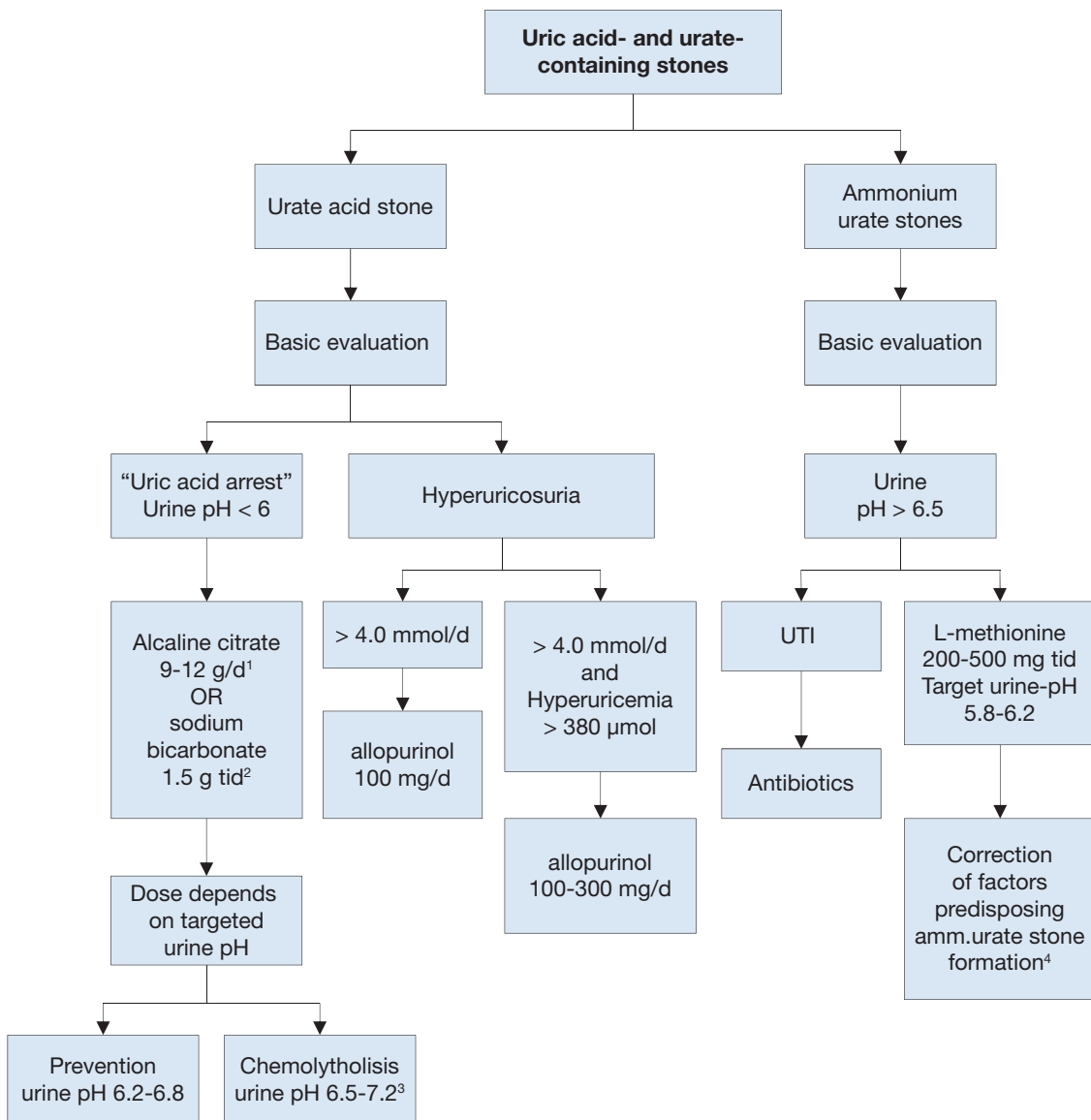
^{1} d: day.
^{2} tid: three times a day.
^{3} A higher pH may lead to calcium phosphate stone formation.
^{4} In patients with high uric acid excretion, allopurinol may be helpful.

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 [505]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [506].

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 [507, 508]. Proteus mirabilis accounts for more than half of all urease-positive UTIs [509, 510].

4.8.2   ***Specific treatment***
General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [506] short- or long-term antibiotic treatment [511], urinary acidification using methionine [460] or ammonium chloride [512], and advise to restrict intake of urease [513, 514]. For severe infections, acetohydroxamic acid may be an option [513, 514] (Figure 4.6), however, it is not licensed/available in all European countries.

4.8.3   ***Recommendations for therapeutic measures of infection stones***

Recommendations for therapeutic measures	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, 2 or 3 times daily to ensure urinary acidification.	3	B
Prescribe methionine, 200-500 mg, 1-3 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
Caliceal diverticulum
Ureteropelvic junction obstruction

Table 4.10: Most important species of urease-producing bacteria

Obligate urease-producing bacteria (> 98%)
•   *Proteus spp.*
•   *Providencia rettgeri*
•   *Morganella morganii*
•   *Corynebacterium urealyticum*
•   *Ureaplasma urealyticum*
Facultative urease-producing bacteria
•   *Enterobacter gergoviae*
•   *Klebsiella spp.*
•   *Providencia stuartii*
•   *Serratia marcescens*
•   *Staphylococcus spp.*
CAUTION: 0-5% of *Escherichia coli, Enterococcus spp*. and *Pseudomonas aeruginosa* strains may produce urease.

Figure 4.6: Diagnostic and therapeutic algorithm for infection stones

```
                    ┌─────────────────────────┐
                    │     Infection stones    │
                    │  (Struvite carbon apatite│
                    │    Ammonium urate¹)     │
                    └───────────┬─────────────┘
                                │
                    ┌───────────▼─────────────┐
                    │     Basic evaluation    │
                    └───────────┬─────────────┘
                                │
          ┌─────────────────────┼─────────────────────┐
          │                     │                     │
  ┌───────▼────────┐   ┌────────▼────────┐   ┌────────▼─────────┐
  │    Urease      │   │    Treatment    │   │   Urinary pH     │
  │   producing    │   │                 │   │ (Carbon apatite  │
  │    bacteria    │   │                 │   │     > 6.8        │
  │                │   │                 │   │  Struvite > 7.2) │
  └────────────────┘   └────────┬────────┘   └──────────────────┘
                                │
     ┌──────────────┬───────────┼────────────────┬──────────────┐
     │              │           │                │              │
┌────▼─────┐  ┌─────▼─────┐  ┌──▼──────┐  ┌───────▼──────┐
│ Complete │  │Antibiotics│  │  Urine  │  │   Urease     │
│ surgical │  │           │  │acidific-│  │ inhibition*  │
│ removal  │  │           │  │ ation   │  │              │
│is mandatory│ │           │  │         │  │              │
└────┬─────┘  └─────┬─────┘  └─┬─────┬─┘  └──────┬───────┘
     │              │          │     │           │
┌────▼─────┐  ┌─────▼─────┐ ┌──▼──┐ ┌▼────┐ ┌────▼────┐
│Percutaneous│ │ Short or │ │Ammon-│ │Methi-│ │  AHA²   │
│chemolysis │  │long course│ │ium  │ │onine │ │15 mg/kg/│
│may be a   │  │           │ │Chlor-│ │200-500│ │  day    │
│useful     │  │           │ │ide   │ │mg    │ │         │
│adjunct    │  │           │ │1 g bid│ │1-3   │ │         │
│           │  │           │ │or tid│ │times/d│ │         │
└──────────┘  └───────────┘ └──────┘ └──────┘ └─────────┘
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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, 515]. 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 [516].
- There is no role for genotyping patients in the routine management of cystinuria [517, 518].
- 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 [519].
- 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-h urinary cystine excretion confirms the diagnosis in the absence of stone analysis.
- Levels above 30 mg/day are considered abnormal [520, 521].

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 [522].

A high level of diuresis is of fundamental importance, aiming for a 24-h urine volume of $\geq$ 3 L [523]. 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/m^2 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
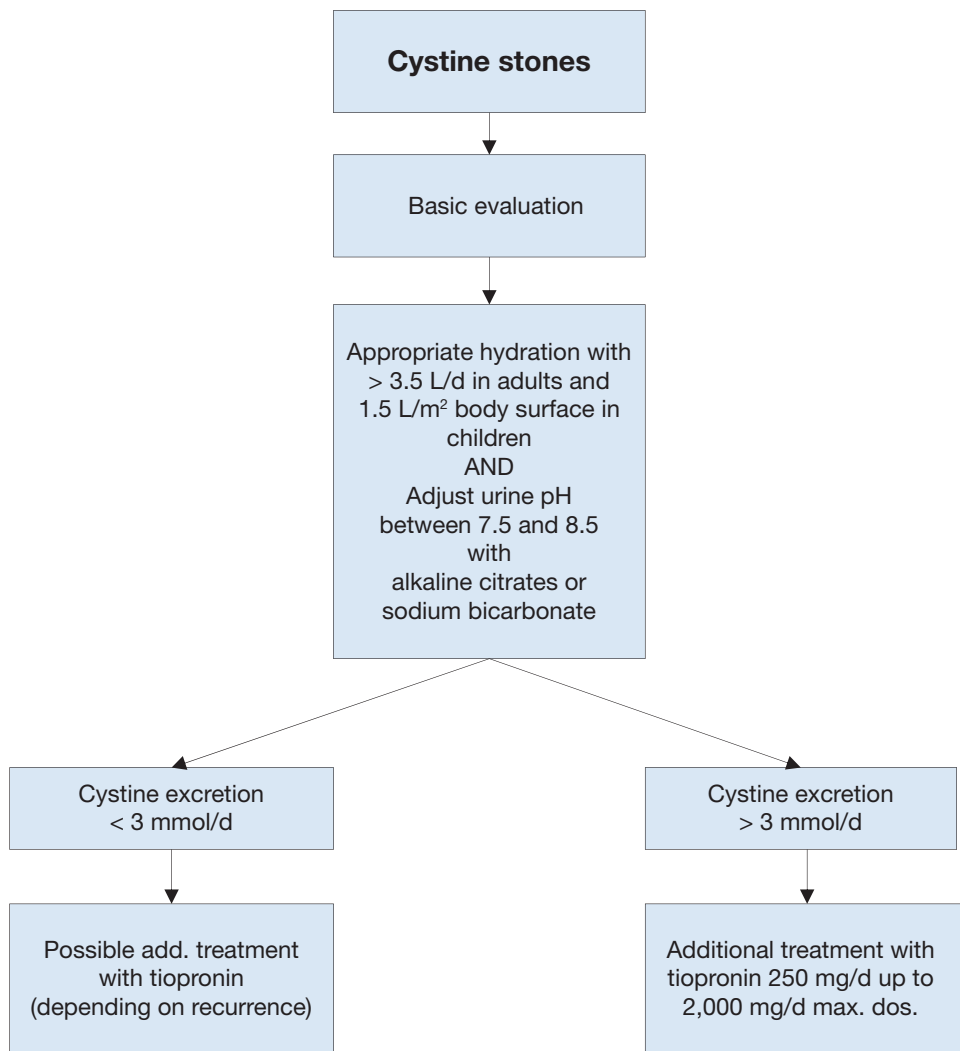
4.9.3 Recommendations for the treatment of cystine stones

Therapeutic measures	LE	GR
Urine dilution Advise patients to increase their fluid intake so that 24-h 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 2 or 3 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-Dihydroxyandenine stones and xanthine stones [17]

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 [47]
Drug stones are induced by pharmacological treatment [524] (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 *Proteous 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 [223].

4.13   Unknown stone composition [16]
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 [525, 526].

Following this programme, the most probable stone type can be assumed and specific patient evaluation can follow. However, if any expulsed 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	• Stone history (former stone events, family history) • Dietary habits • Medication chart
Perform diagnostic imaging	• Ultrasound in the case of a suspected stone • Unenhanced helical CT • (Determination of Hounsfield units provides information about the possible stone composition)
Perform a blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid
Perform a urinalysis	• Urine pH profile (measurement after each voiding, minimum 4 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)

Further examinations depend on the results of the investigations listed above.

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6.   CONFLICT OF INTEREST

All members of the Urolithiasis 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://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
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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 Guidelines document addresses a number of common clinical pathologies in paediatric urological practice, but 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.

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. Also a number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal are available [1, 2]. 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 with subsequent partial updates in 2005, 2006, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015 and this 2016 publication which 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 2016 publication:

- Section 3.2 - Undescended testes (former Cryptorchidism chapter): complete update (prior to print publication)
  Two new figures have been inserted: Figure 1: Classification of undescended testes and Figure 2: Treatment of unilateral non-palpable undescended testes
- Section 3.4 - Acute scrotum in children: The literature has been updated and minor text revisions made
- Section 3.5 - Hypospadias: The literature has been updated extensively
- Section 3.7 - Varicocele in children and adolescents: The literature has been updated extensively
- Section 3.11 - Vesicoureteric reflux literature has been updated
- Section 3.12 - Urinary stone disease literature has been updated

1.5.1 New and changed recommendations

3.2.7 Recommendation for the management of undescended testes

Recommendation	LE	GR
In case of bilateral undescended testes, endocrine treatment is recommended.	4	C

Section 3.6.5 Congenital penile curvature

Recommendation	LE	GR
Diagnose congenital penile curvature during hypospadias or epispadias repair using an artificial erection.	4	B
Perform surgery to treat congenital penile curvature.	4	B

3.7.5 Summary of evidence and recommendations for the management of varicocele

Recommendations	LE	GR
Examine varicocele in the standing position and classify into three grades.	4	A
Use scrotal US 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 US to exlude a retroperitoneal mass.		

US = ultrasound.

3.9.5 Recommendation for the management of day-time lower urinary tract conditions

Recommendation	LE	GR
If present, treat BBD bowel dysfunction first, before treating the LUT condition.	2	B

BBD = Bladder Bowel Dysfunction; LUT = lower urinary tract.

3.11.6 Recommendations for the management of neurogenic bladder

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

Recommendations	LE	GR
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

1.5.2 A summary of evidence has been included in the following sections:

- Section 3.2.7 - A summary of evidence has been added to Chapter 3.2 – Undescended testes.
- Section 3.3.4 – A summary of evidence has been added to Chapter 3.3 – Hydrocele.
- Section 3.4.4 – A summary of evidence has been added to Chapter 3.4 – Acute scrotum.
- Section 3.6.4 – A summary of evidence has been added to Chapter 3.6 – Congenital penile curvature.
- Section 3.7.5– A summary of evidence has been added to Section 3.7 – Varicocele in children and adolescents.
- Section 3.9.5 – A summary of evidence has been added to Section 3.9 – Day-time lower urinary tract symptoms.
- Section 3.10.5 – A summary of evidence has been added to Section 3.10 – Monosymptomatic enuresis.
- Section 3.11.6 – A summary of evidence has been added to Section 3.11 – Neurogenic bladder.
- Section 3.13.4 – A summary of evidence has been added to Section 3.13 – Vesicoureteric reflux in childhood.
- Section 3.16.4 – A summary of evidence has been added to Section 3.16 – Disorders of sex development.
- Section 3.17.7 – A summary of evidence has been added to Section 3.17 – Posterior urethral valves.

2. METHODS

These Guidelines were compiled based on current literature following a systematic 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 current 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 [3]. 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:

1. What are the benefits and harms of antibiotic prophylaxis compared with observation for neonatal hydronephrosis? [4].
2. What are the benefits and harms of hormonal manipulation prior to definitive surgical therapy for primary hypospadias?
3. What are the short-term and long-term benefits and harms of varicocoele 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 3 years. The incidence of phimosis is 8% in 6-7 year olds and just 1% in males aged 16-18 years [5].

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) [5]. Balanitis xerotica obliterans, also termed lichen sclerosis, has been recently found in 17% of boys younger than 10 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 [6] (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 well-visible meatus and free partial retraction [7]. 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 fraenulum 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% [8-11] (LE: 1b; GR: A). A recurrence rate up to 17% can be expected [12]. This treatment has no side effects and the mean bloodspot cortisol levels are not significantly different from an untreated group of patients [13] (LE: 1b). The hypothalamic pituitary-adrenal axis was not influenced by local corticoid treatment [14]. Agglutination of the foreskin does not respond to steroid treatment [10] (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 [15]. 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 [16]. In the same session, adhesions are released and an associated fraenulum 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 [17-20] (LE: 2b; GR: B). Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [21] (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 [22]. 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 [23, 24]. Circumcision can be performed in children with coagulopathy with 1-5% suffering complications (bleeding), if haemostatic agents or a diathermic knife are used [25, 26]. Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason and also taking into account epidemiological and social aspects [27-31] (LE: 1b; GR: B).

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 [32, 33] (LE: 3-4; GR: B-C). 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 on 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 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 in case manual reposition has failed.	3	B
Routine neonatal circumcision is not recommended to prevent penile carcinoma.	2b	B

UTI = urinary tract infection.

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 [34]. This congenital malformation may affect both sides in up to 30% of cases [35]. 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 [36].

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 [37]. 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 the first step of any surgical procedure for undescended testes.

Figure 1: Classification of undescended testes
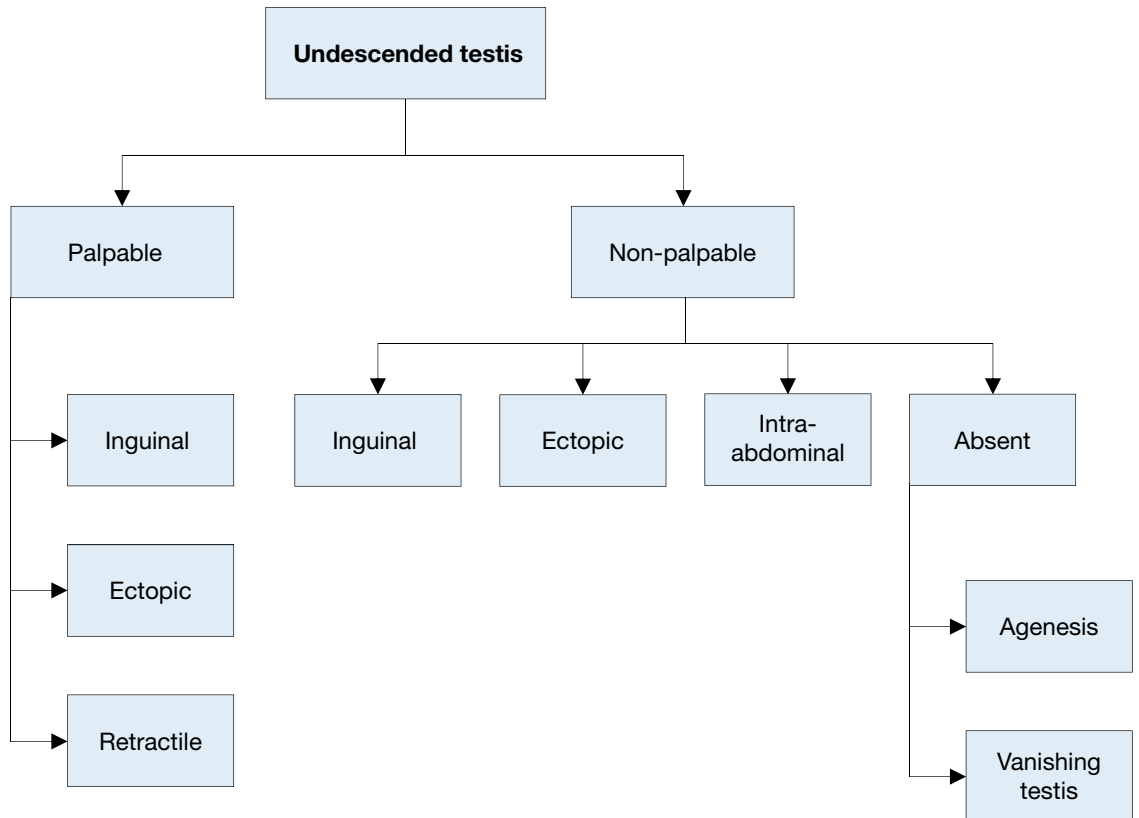
3.2.2.1   Palpable testes
Undescended testes
A true undescended testis is on its normal path of descent but is halted on its way down to the scrotum. Depending on the location, the testes may be palpable or not, as in the case of testes arrested in the inguinal canal.

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 a 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 [38]. 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 [39].

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 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 [40].

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 [41]. 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 [42]. 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 [43]. Nevertheless, this does not preclude surgical exploration since the sign of compensatory hypertrophy is not specific enough [44].

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 [45].

3.2.3.3 *Imaging studies*
Imaging studies cannot determine with certainty that a testis is present or not [46]. Ultrasound (US) lacks the diagnostic performance to detect confidently the testis or positively establish the absence of an intra-abdominal testis [47].

Consequently, the use of different imaging modalities, such as US or magnetic resonance imaging (MRI) [48], 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) [49].

3.2.4 *Management*
Treatment should be started at the age of 6 months. After that age, undescended testes rarely descend [50]. Any kind of treatment leading to a scrotally positioned testis should be finished by 12 months, or 18 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 [51]. 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 [52].

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 [53].

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% [54]. However, it must be taken into account that almost 20% of these descended testes have the risk of re-ascending later [53]. 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% in non-responders to monotherapy [56]. The Panel consensus is that endocrine treatment to achieve testicular descent is not recommended (LE: 4; GR: C).

hCG
hCG 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 14 days [57]. Similar response rates were achieved with 500 IU once weekly and 1.50 IU three times weekly [58]. 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 [59].

GnRH analogues
GnRH 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/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 [60].

3.2.4.1.2 Medical therapy for fertility potential
Hormonal treatment may improve fertility indices [61] 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 [62]. 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 [63].

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 [64].

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 [65]. 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 6 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 18 months at the latest [51]. In addition, early orchidopexy can be followed by partial catch-up testicular growth, which is not the case in delayed surgery [66]. All these findings recommend performing early orchidopexy between the ages of 6 and 12 months [50].

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 [67].

3.2.4.2.1.1 Inguinal orchidopexy
Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% [68]. 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 [69]. 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 epididimys to the testis can be judged and decribed 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 [70]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [71]. 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 [72].

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 [73]. 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 [74]. 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% [67].

3.2.4.2.2   Non-palpable testes

For non-palpable testes, surgery must clearly determine whether a testis is present or not [75]. 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 [76]. Subsequent removal or orchidolysis and orchidopexy can be carried out using the same approach to achieve the therapeutic aims [77]. Some tend to start with inguinal surgical exploration, with possible laparoscopy during the procedure [78]. 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 [79].

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%) [80].

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 [81]. A peeping testis can be placed down in the scrotum laparoscopically or via an inguinal incision [82]. 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 [83]. Under such circumstances, a Fowler–Stephens orchidopexy may be an option [84] (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 [85]. Due to the nature of these approaches that the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [86]. 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 [87]. The advantages of two-stage orchidopexy, with the second part done usually 6 months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility [88]. In addition preservation of the gubernaculum may also decrease the chance of testicular atrophy [89].

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 [90].

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 [91].

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% [92].

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
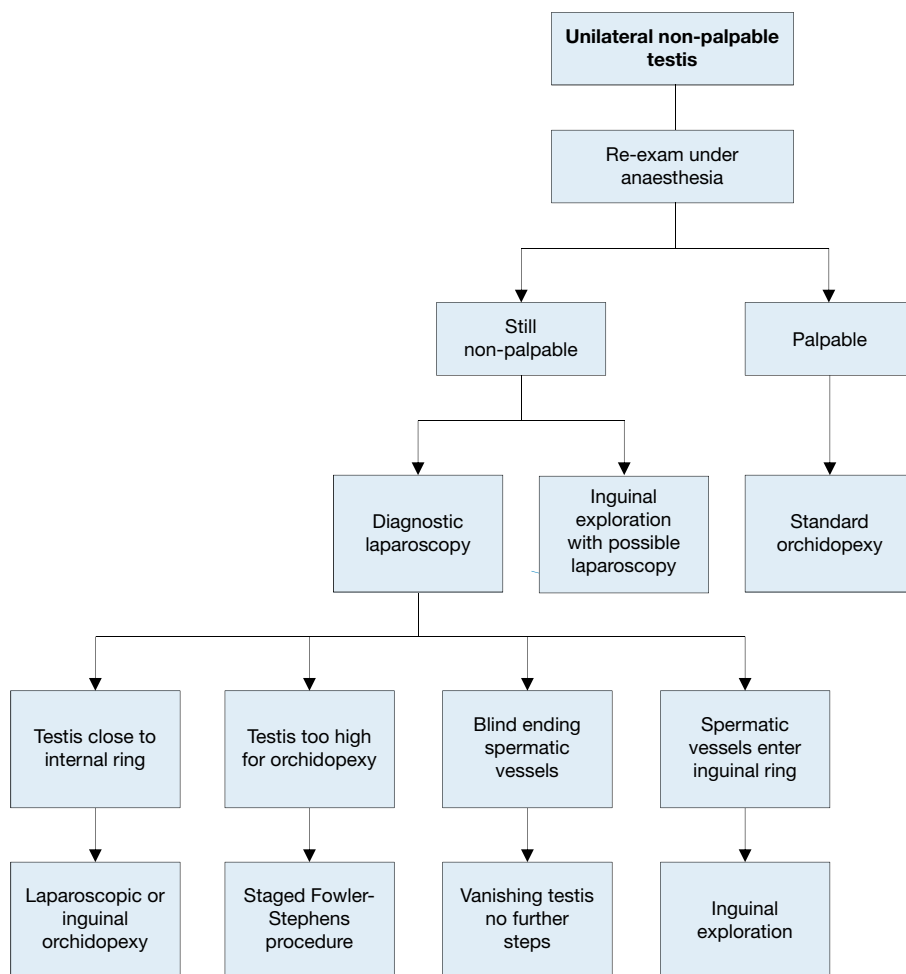
3.2.5 *Undescended testes and fertility*

The association of undescended testes with compromised fertility [93] is extensively discussed in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [94], Leydig cell diminution, and testicular fibrosis [95].

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 [96].

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 levels in men who underwent orchidopexy at age 2 years compared to individuals who had surgery later, which is indicative of a benefit of earlier orchidopexy [97]. 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 [98].

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 [95].

In summary, regarding preservation of fertility potential, early surgical correction of undescended testes is highly recommended before 12 months of age, and by 18 months at the latest [51].

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 [99].

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 [100].

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 [101].

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

Recommendation	LE	GR
Boys with retractile testes do not need medical or surgical treatment, but close follow-up until puberty is recommended.	2a	A
Surgical orchidolysis and orchidopexy are strongly recommended before the age of 12 months, and by 18 months at the latest.	2b	B
Male neonates with bilateral non-palpable testes should be evaluated for possible DSDs.	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
Hormonal therapy, either in an adjuvant or neo-adjuvant setting, is not routinely recommended. Patients have to be evaluated on an individual basis.	2a	C
In case of bilateral undescended testes, endocrine treatment is recommended.	4	C
For an undescended testis in a post-pubertal boy or older, with a normal contralateral testis, removal should be discussed with the patient/parents because of the theoretical risk of a later malignancy.	3	B

DSD = disorders of sex development.

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 tunica vaginalis [102]. 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 [103]. 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 [104]. 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 [105]. Non-communicating hydroceles, based on an imbalance between the secretion and reabsorption 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 [106, 107]. 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 non-tender. 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, the surgical treatment of hydrocele is not indicated within the first 12 months because of the tendency for spontaneous resolution [108] (LE: 2; GR: B). Little risk is taken by initial observation as progression to hernia is rare and does not result in incarceration [108]. Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology [109, 110] (LE: 2; GR: B). Persistence of a simple scrotal hydrocele beyond 12 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 [111].

The question of contralateral disease should be addressed by both history and physical examination at the time of initial consultation (LE: 2) [112]. 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 [113]. 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 [102, 107, 109] (LE: 4; GR: C). In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low (0.3%) (LE: 3; GR: B). Sclerosing agents should not be used because of the risk of chemical peritonitis in communicating processus vaginalis peritonei [107, 109] (LE: 4; GR: C). 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 12 months due to the tendency for spontaneous resolution. Little risk is taken by initial observation asprogression 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 12 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 US 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

US = ultrasound.

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 [114-119]. 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) [120-132]. Trauma can also be a cause of acute scrotum as it can relate to post traumatic haematomas, testicular contusion, rupture dislocation or torsion [133-138]. 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 [139].

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. Acute epididymitis affects two age groups: < one year and twelve to fifteen years [117, 140, 141]. Acute epididymitis is found most often (37-64.6%) in boys with acute scrotum [114, 115, 118, 119]. One study predicted the annual incidence of epididymitis around 1.2 per 1,000 children [142]. Perinatal torsion of the testis most often occurs prenatally. Perinatal torsion occurs after birth in 25% of the cases. Bilateral torsion comprises 11-21% of all perinatal cases [143]. 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 newborn torsion. The duration of symptoms is shorter in testicular torsion (69% present within twelve hours) compared to torsion of the appendix testes (62%) and acute epididymitis (31%) [116, 117, 141].

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 [141]. An abnormal position of the testis is more frequent in testicular torsion than epididymitis [116]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [140, 144] (LE: 3; GR: C). Fever occurs 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 [115, 116, 140, 145].

In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [114-119, 140, 145]. A positive urine culture is only found in a few patients with epididymitis [118, 140, 145, 146]. 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% [147-152] (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 [149, 153]. 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 [149]. 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% [149, 154] (LE: 2; GR: C).

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to US [155-158]. 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 [145].

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 [159]. 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 [118, 140, 142].

Near-infrared spectroscopy has been used to diagnose testicular torsion in adults [160]. This non-invasive optical technique estimates the oxygenation of the spermatic cord tissue that is reduced in testicular torsion. However there is only one case report of its use in childhood in the literature [161].

3.4.3   *Management*
3.4.3.1   *Epididymitis*
In pre-pubertal boys, the aetiology is usually unclear, with an underlying pathology of 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 [142, 162]. Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3; GR: C). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required [163].

Torsion of the appendix testis can be managed non-operatively with the use of anti-inflammatory analgesics (LE: 4; GR: C). 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 [152].

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 11 patients who had reported pain relief after manual detorsion [164, 166].

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°. In cases of incomplete torsion (180-360°), 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° and symptom duration > 24 hours [168].

Early surgical intervention with detorsion (mean torsion time < 13 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 recent 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 common recommendation about the preferred type of fixation and suture material; however, many urologists currently use a Dartos pouch orchidopexy with non-absorbable suture material [171].

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 [172-176].

3.4.4 Follow-up

Patients require follow-up mainly for fertility issues, hormonal consequences and cancer.

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 [177].

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 < 13 h) with detorsion was found to preserve fertility, but a prolonged torsion period (mean 70 h) 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 the post-ischaemia-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 follicle-stimulating hormone (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 Testicular cancer

There may be a 3.2-fold increased risk of developing a testis tumour 6-13 years after torsion. However, two of nine reported cases had torsion of a tumour-bearing testis and four had a tumour in the contralateral testis [167].

3.4.5 Summary of evidence and recommendations for the management of acute scrotum in children

Summary of evidence	LE
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
Testicular torsion is a paediatric emergency and intervention should not be delayed.	3	A
In neonates, also explore the contralateral scrotum.	3	C
Use doppler US to evaluate acute scrotum without delaying the surgical exploration.	2a	A
For direct visualisation of spermatic cord twisting use high-resolution US.	3	C
Use conservative treatment to manage torsion of the appendix testis. Perform surgical exploration in equivocal cases and in patients with persistent pain.	3	C
Perform urgent surgical exploration in all cases of testicular torsion within 24 hours of symptom onset.	3	C

US = ultrasound.

3.5 Hypospadias
3.5.1 *Epidemiology, aetiology and pathophysiology*
3.5.1.1 Risk factors

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [178] (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 [179] (LE: 2b; GR: B).
- An additional member with hypospadias is found in 7% of families [180].
- Endocrine disorders can be detected in rare cases.
- Babies of young or old mothers and babies with a low birth weight have a higher risk of hypospadias [180].
- A significant increase in the incidence of hypospadias over the last 25 years suggests a role for environmental factors (hormonal disruptors and pesticides) [181-184]. Though this information has been questioned [185].
- The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in offspring [186] (LE: 2a; GR: B).

A Dutch case-control study confirmed that genetic predisposition possibly plays a role in anterior and middle hypospadias, in contrast, the posterior phenotype was more often associated with pregnancy-related factors, such as primiparity, preterm delivery, and being small for gestational age. Hormone-containing contraceptive use after conception increased the risk of middle and posterior hypospadias, while multiple pregnancies were associated with the posterior form in particular [187] (LE: 2a).

3.5.2 *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 much more severe after skin release.

3.5.3 *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 the associated anomalies of the upper- or lower urinary tract were not confirmed in a systematic literature review [188] (LE: 3).

3.5.4 **Management**

Differentiation between functionally necessary and aesthetically feasible operative procedures is important for therapeutic decision-making.

The functional indications for surgery are:
• Proximally located 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.

The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the neomeatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance of the genitalia [181] (LE: 4; GR: C) (see Figure 3).

The use of magnifying spectacles and fine synthetic absorbable suture materials (6/0-7/0) is required. As in any penile surgery, exceptional prudence should be adopted with the use of cautery. Knowledge of a variety of surgical reconstructive techniques, wound care and post-operative treatment are essential for a satisfactory outcome. 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 [189]. The effect of pre-operative hormonal stimulation on operative outcomes after hypospadias repair remains unclear according to systematic review [190, 191].

3.5.4.1 **Age at surgery**

The age at surgery for primary hypospadias repair is usually 6-18 (24) months [181] (LE: 4; GR: C). However, earlier repair between 4 and 6 months of age has been reported recently [192, 193] (LE: 3; GR; B). Age at surgery is not a risk factor for urethroplasty complication in pre-pubertal tubularised incised plate urethroplasty (TIP) repair [192] (LE: 2b).

3.5.4.2 **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% [194]. The urethral plate has well vascularised connective tissue and does not cause curvature in most cases. The residual curvature is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal midline plication or orthoplasty or ventral corporotomies with or without grafting [195, 196] (LE: 2b; GR: B). No systematic review or meta-analyses related to this subject is currently available.

3.5.4.3 **Preservation of the well-vascularised urethral plate**

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 [197]. Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection [196] (LE: 2b; GR: B). Urethral plate elevation and urethral mobilisation with TIP resulted in focal devascularisation of the neourethra with symptomatic stricture development [198] (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 that a midline-relaxing incision of the plate, followed by reconstruction according to the Snodgrass-Orkiszewski technique, is performed in distal hypospadias, as well as in proximal hypospadias (though the complication rate is higher) [199-203].

The onlay technique is preferred in proximal hypospadias and if a plate is unhealthy or too narrow [194]. For distal forms of hypospadias, a range of other techniques are available (e.g. TIP, Mathieu, urethral advancement) [204] (LE: 2b; GR: B).

If the continuity of the urethral plate cannot be preserved, a modification of the tubularised flap,

such as a tube-onlay, an inlay-onlay flap, or onlay flap on albuginea is used to prevent urethral stricture [205-207] (LE: 3). In this situation, as well as in severe scrotal or penoscrotal hypospadias, the Koyanagi technique or two-stage procedure may be preferable, reported complication rate is 61 and 68%, respectively [208, 209] (LE: 3; GR: C). The use of dorsal inlay skin grafts may allow an increased number of single-stage repairs to be performed [210].

3.5.4.4 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 needs of the patient.

Figure 3: Algorithm for the management of hypospadias
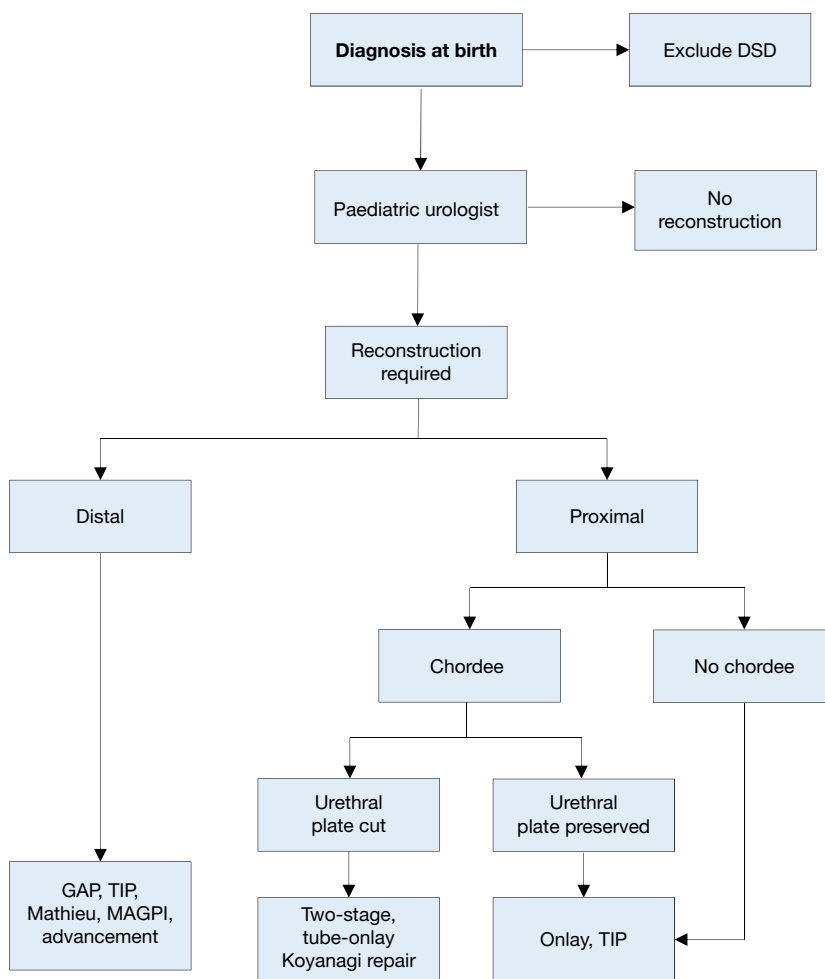
DSD = disorders of sex development; GAP = glans approximation procedure; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

3.5.4.5 Urethral reconstruction
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 may be used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. However, in the TIP repair, the parents should be advised that use of a preputial dartos flap reduces the fistula rate [199, 200] (LE: 2b; GR: B).

3.5.4.6 Urine drainage and wound dressing
Urine is drained with a transurethral dripping stent, or with a suprapubic tube. Some surgeons use no drainage after distal hypospadias repair. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures [211] (LE: 4; GR: C). Post-operative prophylaxis after hypospadias repair is controversial [212, 213] (LE: 2b). A large variety of duration of stenting and dressing is described. No recommendation can be given due to the low level of evidence.

3.5.4.7 Outcome

A literature review on distal TIP urethroplasty found significant clinical heterogeneity with some limitations to the comparability of the data; one should expect a predictable outcome with complication rates below 10% (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) [214, 215]. A systematic review of the Mathieu and TIP repairs of distal hypospadias found similar incidence of fistula (3.4-3.6%), and higher incidence of meatal stenosis in TIP (3.0% vs. 0.6% in Mathieu) after six to twelve months follow-up [216]. Another systematic review and meta-analysis found no difference in fistula, meatal stenosis or glans dehiscence, but better cosmesis in TIP repair [203, 217].

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 [194]. 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 [218]. Low surgeon volume independently increases the risk of fistula, stricture or diverticulum repair [215] (LE: 3). Ventral corporeal grafting for severe penile curvature gives good long-term results and safety profiles for erectile function [219] (LE: 2b).

3.5.5 Follow-up

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfuntions and recurrent penile curvature. Up to half of complications requiring reoperation present after the first year post-operatively [220] (LE: 2b).

Overall, between 7% and 67% of patients operated on for hypospadias end up with an obstructive flow (24.6% in TIP). These children should be followed until adulthood to clarify the clinical significance. Spontaneous improvement has been described [221, 222] (LE: 2a). Urine flow is significantly lower in patients after hypospadias surgery, especially in those who had corrected chordee, than in controls, but without significant association with lower urinary tract symptoms (LUTS) [223] (LE: 2a).

Objective scoring systems have been developed in order to evaluate the results of hypospadias surgery [224] (LE: 2b) and cosmetic appearance (HOPE) [225] (LE: 2a). The Pediatric Penile Perception Score 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 [226] (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 [227, 228] (LE: 2a-b).

3.5.6 Summary of evidence and recommendations for the management of hypospadias

Summary of evidence	LE
The suggested age at surgery for primary hypospadias repair is 6-24 months.	4
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
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
Differentiate between functionally necessary (functional indications) and aesthetically feasible operative procedures (psychological, cosmetic indications).	A
Ensure that parents receive thorough pre-operative counselling.	A
For distal hypospadias, use original and modified tubularised incised plate urethroplasty or Mathieu procedure. Use the onlay urethroplasty or two-stage procedures in more severe hypospadias. A treatment algorithm is presented (see Figure 3).	B
Ensure long-term follow-up, up to adolescence, to detect urethral stricture, voiding dysfunctions and recurrent penile curvature.	A
Use the new 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

Penile curvature may be ventral, dorsal or lateral. Most ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies [229]. Similarly, dorsal curvature is mostly associated

with exstrophy/epispadias complex [230]. Isolated curvature is not frequent with an incidence of 0.6 % [231] (LE: 2) and is caused by asymmetry of the cavernous bodies [229, 232]. Curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood [233] (LE: 4).

3.6.2 Diagnostic evaluation
Diagnosis is made during hypospadias or epispadias repair using an artificial erection [234]. The isolated anomaly is usually not recognised until later in childhood because the appearance of the penis is normal. The curvature is only observed during erections.

3.6.3 Management
The treatment is surgical. An artificial erection is used to determine the degree of curvature and to check symmetry after the repair [234].

In hypospadias, chordee related to the tethering of the ventral skin and to the spongiosal pillars is first released. Only in a few cases, the penile curvature is caused by a short urethral plate, which should be cut. To repair the corporeal angulation in the isolated curvature, or curvature associated with hypospadias, different techniques of plication of corpora cavernosa (orthoplasty) are used [233].

In exstrophy/epispadias complex, a combination of complete release of the urethral body from the corpora and a different kind of corporoplasty with or without corporotomy is usually necessary to achieve a straight penis [235, 236].

3.6.4 Summary of evidence and recommendations for the management of congenital penile curvature

Summary of evidence	LE
Congenital penile curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood.	4

Recommendations	LE	GR
Diagnose congenital penile curvature during hypospadias or epispadias repair using an artificial erection.	4	B
Perform surgery to treat congenital penile curvature.	4	B

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 10 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 [237-239].

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 [240, 241]. The average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a recent meta-analysis [242] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [243] (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise [244]. The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [245-247] [248] (LE: 1).

3.7.2 Classification systems
Varicocele is classified into 3 grades:
- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);

- Grade II - palpable (palpable without the Valsalva manoeuvre);
- Grade III - visible (visible at distance) [249].

3.7.3 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 [250]. 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 [251] (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 [246, 252].

3.7.4 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 [253] (LE: 4).

The recommended indication criteria for varicocelectomy in children and adolescents are [238]:
- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- symptomatic varicocele [253].

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available [254]. 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 [255-258].

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 [255, 257]. 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 [243, 255, 256, 259] (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [255, 257, 260, 261]. Intrascrotal application of isosulphan blue was recommended to visualise the lymphatic vessels [262, 263]. 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 [264, 265].

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 [266, 267]. 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 [238, 266, 267] (LE: 2).

3.7.5 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 US 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 US to exlude a retroperitoneal mass.		
Perform surgery for: • 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

US = ultrasound.

3.8 Urinary tract infections in children
3.8.1 Epidemiology, aetiology and pathophysiology
Urinary tract infections (UTIs) represent the most common bacterial infection in children [268-270]. 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 [271-274].

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 [272]. 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 [272-275].

E. coli is found in ~75% of UTIs and is more frequent in community-acquired than nosocomial. 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 [276], however, it is less frequent in community-acquired than in nosocomial UTI [276, 277].

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 [278]. 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 their bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract [279].

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 LUT 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 [280]. 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 postnatal US screening); prior operation; family history; and whether there is constipation or presence of 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). UTI is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic [281-283]. 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 > 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 [284].

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 [285]. However, if the genitalia are not cleaned and culture is delayed, a high incidence of false-positive results (85-99%) can be found [286, 287].

(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 [288]. 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% [288, 289]; however the contamination rate is higher compared to SPA [290].

(3) Bladder catheterisation: In female infants and also in neonates, this technique may be an alternative to SPA, however with a higher contamination rate [291]. 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 < six months, difficult catheterisation, and uncircumcised boys. In children < six months and uncircumcised boys a new, sterile catheter with each repeated attempt at catheterisation may lead to less contamination [292] 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 [292-294]. Using US to assess bladder filling, simplifies SPA and improves the diagnostic yield of obtaining a urine specimen from 60% to 97% [293, 294]. Complications are rare and have been reported in only 0.22% of cases, ranging from transient haematuria to bowel perforation [295]. However, bladder puncture causes more pain than catheterisation in infants < 2 months old [296].

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 periurethral 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 [297].
        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 [289]. 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 4 h in the bladder [289, 298]. 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) [289, 299].

Table 1: Sensitivity and specificity of component of urinalysis, alone and in combination [289]*

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)

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(2) Microscopy: This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of 5 white blood cells (WBCs) per high-power field (25 WBC/μL) [295]. In uncentrifuged urine, > 10 WBC/μL has been demonstrated to be sensitive for UTI [300] and this could perform well in clinical situations [301]. 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 [302]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [289].

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 [274]. The classical definition of > 10^5 cfu/mL of voided urine is still used to define a significant UTI [303, 304]. 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 [305, 306]. 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 [307]**)**

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) [289]. In other studies, renal US revealed abnormalities in up to 37% of cases, whereas voiding cystourethrography (VCUG) showed VUR in 27% of cases [277]. Dilating VUR is missed by US in around one third of cases [308]. Post-void residual urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI. Elevated post-void residual urine volume predictis recurrence of UTIs in toilet-trained children [309].

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 [310] 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. [308, 311]. 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 [312]. 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 [313, 314]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [315]. 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 [316-319]. Treatment of constipation leads to a decrease in UTI recurrence [320-322]. 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 < 2 months, parenteral antibiotic therapy is recommended. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudo-hypoaldosteronism can occur in these cases [323, 324].

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 [280, 325, 326].

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 [289]. Especially in infancy, not all available antibiotics are approved by the national health authorities. 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 [325, 327, 328].

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 [289]. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [276, 280]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [329]. 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 [326, 330-332]. Similar data have been shown for amoxicillin-clavulanate [333], 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 [334].

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 [280]. Parenteral treatment with broad-spectrum antibiotics is preferred. A temporary urinary diversion (suprapubiccystostomy 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 [335], and intravenous and oral therapy tailored to the pathogen identified in culture is recommended [336].

Figure 4: Algorithm for disease management of first febrile UTI
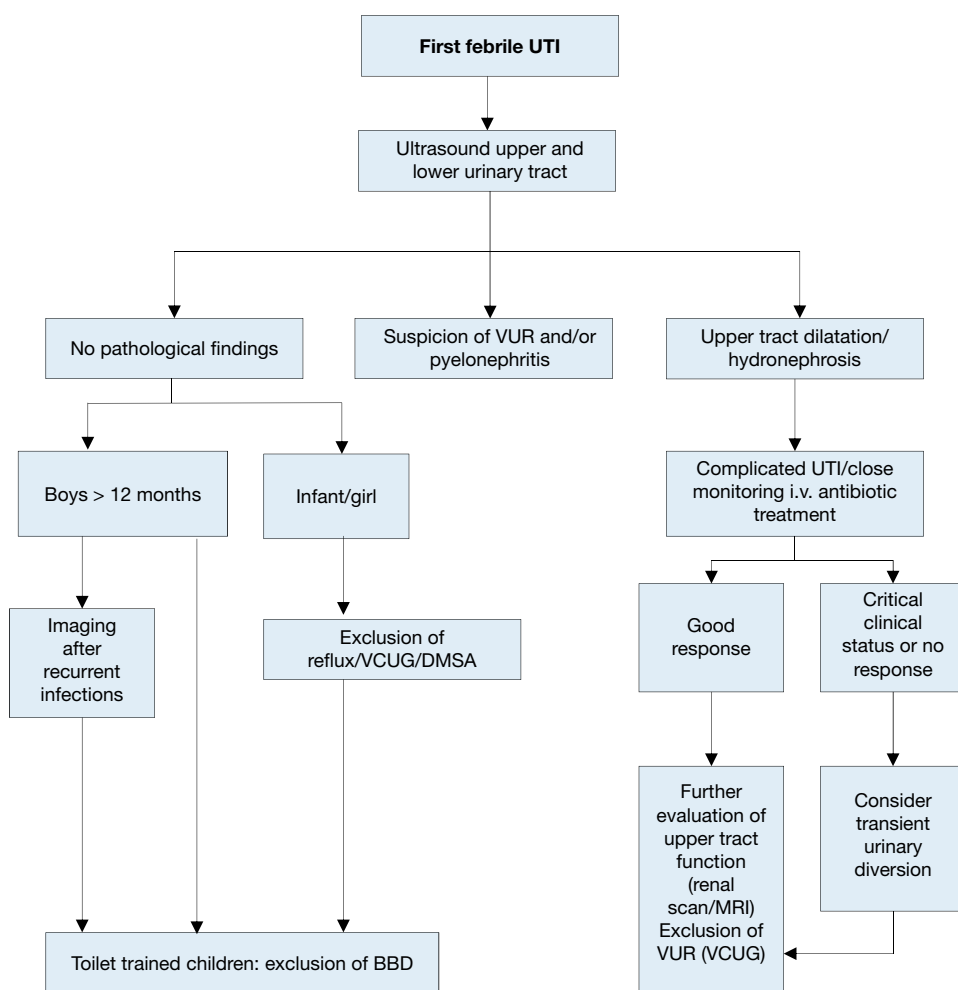
BBD = Bladder Bowel Dysfunction; DMSA = technetium^{99}-labelled dimercaptosuccinic acid; MRI = magnetic resonance imaging; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.

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 [337]. There are upcoming reports of UTIs caused by extended spectrum ß-lactamase-producing enterobacteriaceae (ESBL) in children. In one study from Turkey, 49% of the children < 1 year of age and 38% of those > 1 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% [338]. 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 [339].

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 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 Amoxicillin Amoxicillin/clavulanic acid (parenteral) Amoxicillin/clavulanic acid (oral) Piperacillin	100-200 mg/kg *(Adolesc.: 3-6 g)* 50-100 mg/kg *(Adolesc.: 1.5-6 g)* 60-100 mg/kg *(Adolesc.: 3.6-6.6 g)* 45-60 mg/kg *(Amoxicillinfraction)* *(Adolesc.: 1500 + 375 mg)* 300 mg/kg	i.v. in 3 D i.v. in 3-4 D p.o. in 2-3 D[1] p.o. in 2-3 D i.v. in 3 D i.v. in 3 D p.o. in 3 D p.o.in 3 D i.v. in 3-4 D	Ampicillin and Amoxicillin are not eligible for calculated therapy
Tobramycin Gentamicin	5 mg/kg *(Adolesc.: 3-5 mg/ kg, max.0.4 g)* 5 mg/kg *(Adolesc.: 3-5 mg/ kg, max. 0.4g)*	i.v. in 1 D 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) Children and adolesc. (1-17 years of age): 20-40 mg/kg (max. D 750 mg) (orally)	i.v. in 3 D p.o. in 2 D	Approved in most European countries as second- or third line medication for complicated UTIs, "reserve-antibiotic"!
Nitrofurantoin	3-5 mg	p.o. in 2 D	Contraindicated in the case of renal insufficiency

* Reproduced with permission from the International Consultation on Urological Diseases (ICUD), International Consultation on Urogenital Infections, 2009. Copyright © by the European Association of Urology [340]. Dosage for adolescents in paracentesis, if differing. 1 Infants 2 D, children 1-12 ys. 3 D.

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 days parenterally, for at least 2 days after defervescence, then oral therapy[2] In newborns: parenteral therapy for 7-14 days, then oral therapy[2]	10 (-14) days Newborns 14-21 days	4
Uncomplicated pyelonephritis after 6 months of age	Cephalosporin group 3[2]	Orally (initially parenterally, if necessary)	(7-)10 days	1
Complicated pyelonephritis/ urosepsis (all ages)	Ceftazidime + Ampicillin[1] or Aminoglycoside + Ampicillin[1]	7 days parenterally, then oral therapy[2]	10-14 days	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 12 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 [341-344]. The Australian PRIVENT study demonstrated risk reduction using trimethoprim-sulfamethoxazole in children from birth to 18 years of age who had at least one symptomatic UTI (19% of the placebo group and 13% of the antibiotic group) [330] (see also Chapter 3.13 on Vesico-ureteral reflux).

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 [345]. 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 < 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 of 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 harbouring a 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 to 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 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 (1-3 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 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 VUR after the first episode of febrile UTI, using VCUG or a DMSA-scan first (in case of a positive DMSA-scan, follow-up with VCUG). In boys > 1 year of age, exclude VUR after the second febrile UTI.	2a	B

DMSA = dimercaptosuccinic acid; LUTS = lower urinary tract symptoms; UTI = urinary tract infections; VCUG = voiding cystourethography; VUR = vesicoureteral reflux; WBC = white blood cell.

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 lower urinary tract (LUT) conditions' is the new term used to group together functional incontinence problems in children [346]. 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. BBD 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% [347-351]. This wide variation might reflect the variation in definitions used. In recent studies, bowel dysfunction is observed in > 50 % of children suffering LUT dysfunction [352, 353].

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. LUT 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 [347]. 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) [354, 355].

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 [355]. 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 [356, 357]. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [358, 359].

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 upper urinary tract 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 [360] (LE: 1b; GR: A).

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 [361]. In case of comorbidity due to bowel problems it is advised to treat the bowel first, since bowel problems may sustain any bladder problems [358]. 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 [353] 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 [360] (LE: 1b; GR: A).

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 [320, 361-366]. 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 [367, 368]. In some cases, pharmacotherapy may be added. Antispasmodics and anticholinergics have been shown to be effective, though the level of evidence level was low. Some studies on orthosypathicomimetics have been published with a low level of evidence [369].

A few RCTs have been published, one on tolterodine showed safety but not efficacy [370], while another on propiverine showed both safety and efficacy [371] (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 (GR: B) 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 [372]. Botulinum toxin injection seems promising, but can only be used off-label [373]. 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 [374]. A recent standardisation document of ICCS on treatment of day-time incontinence gives an excellent overview of treatment modalities [354].

*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 LUTD in children.	4	B
Initially offer urotherapy involving: non-invasive training and re-education, and non-invasive neurostimulation.	2	B
If present, treat BBD bowel dysfunction first, before treating the LUT 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 MRI 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

BBD = Bladder Bowel Dysfunction; LUT = lower urinary tract; LUTD = lower urinary tract dysfunction; MRI = magnetic resonance imaging.

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 [375, 376]. 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 [377].

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 [375-377]. Recently, attention has been given to the chronobiology of micturition in which the existence of a circadian clock in kidney, brain and bladder [378] (LE: 1; GR: A).

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 [375]. 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' [377].

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 [379].

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 [380] (LE:1a; GR: A).

3.10.4.2 Alarm treatment

Alarm treatment is the best form for arousal disorder (LE: 1; GR: A). 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 [381].

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 [382, 383] (LE: 1; GR: A). Relapse rates are high after DDAVP discontinuation [379] however recently, structured withdrawal has shown lower relapse rates [384] (LE: 1; GR: A).

In the case of small bladder capacity, treatment with antispasmodics or anticholinergics is possible [379]. 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 [385] (LE: 1; GR: C). Figure 5 presents stepwise assessement and management options for nocturnal enuresis.

Figure 5: Assessment and management of nocturnal enuresis
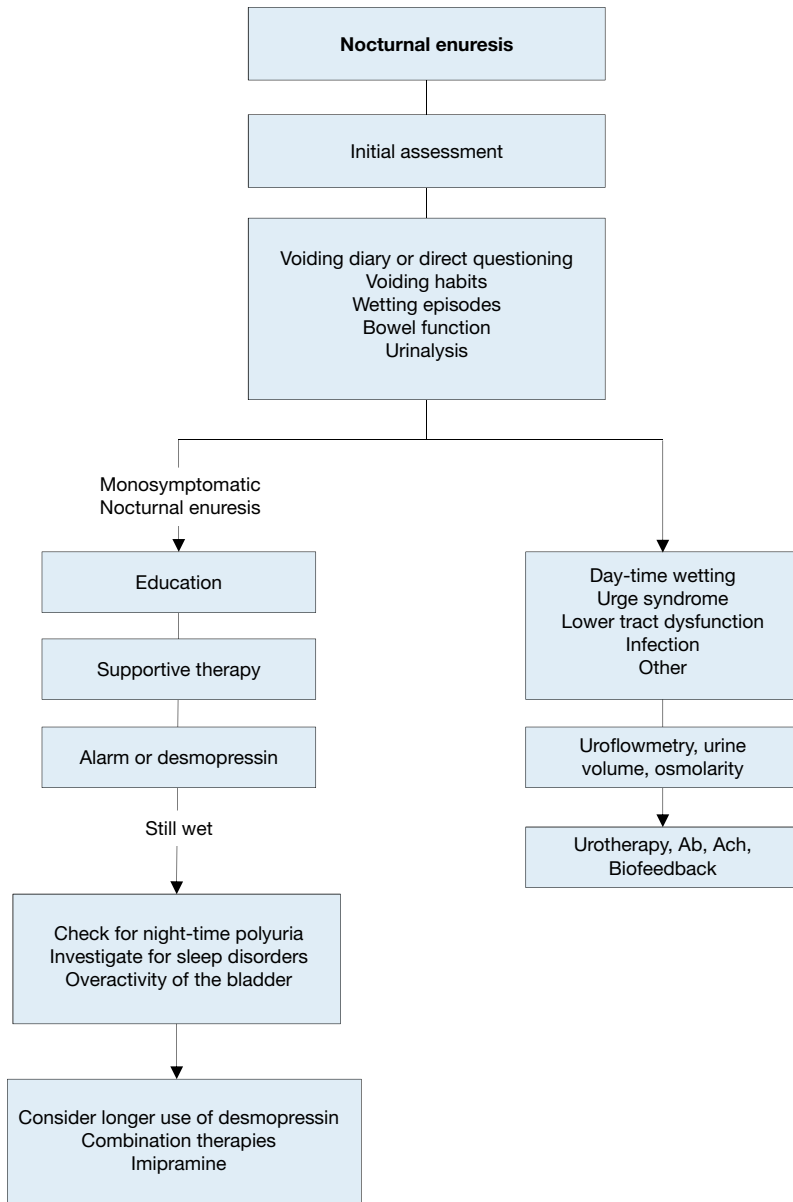
Ab = antibody; Ach = acetylcholine.

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 < 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 should be 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 [386-388].

Neurogenic bladder in children with myelodysplasia presents with various patterns of DSD within 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 upper urinary tracts, but nearly 60% of them develop upper tract deterioration due to infections, bladder changes and reflux [389-392].

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 [393].

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 meningomyelocele, 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 [394-397] (LE: 3; GR: C).

3.11.3.2   Cystometry

Although moderately invasive and dependent on a cooperative 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 [398]. 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 [376].

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 [399-404]. 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 [405-408].

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 [399, 403, 405] (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 [406] (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 [409]. 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 [397].

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 [410].

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
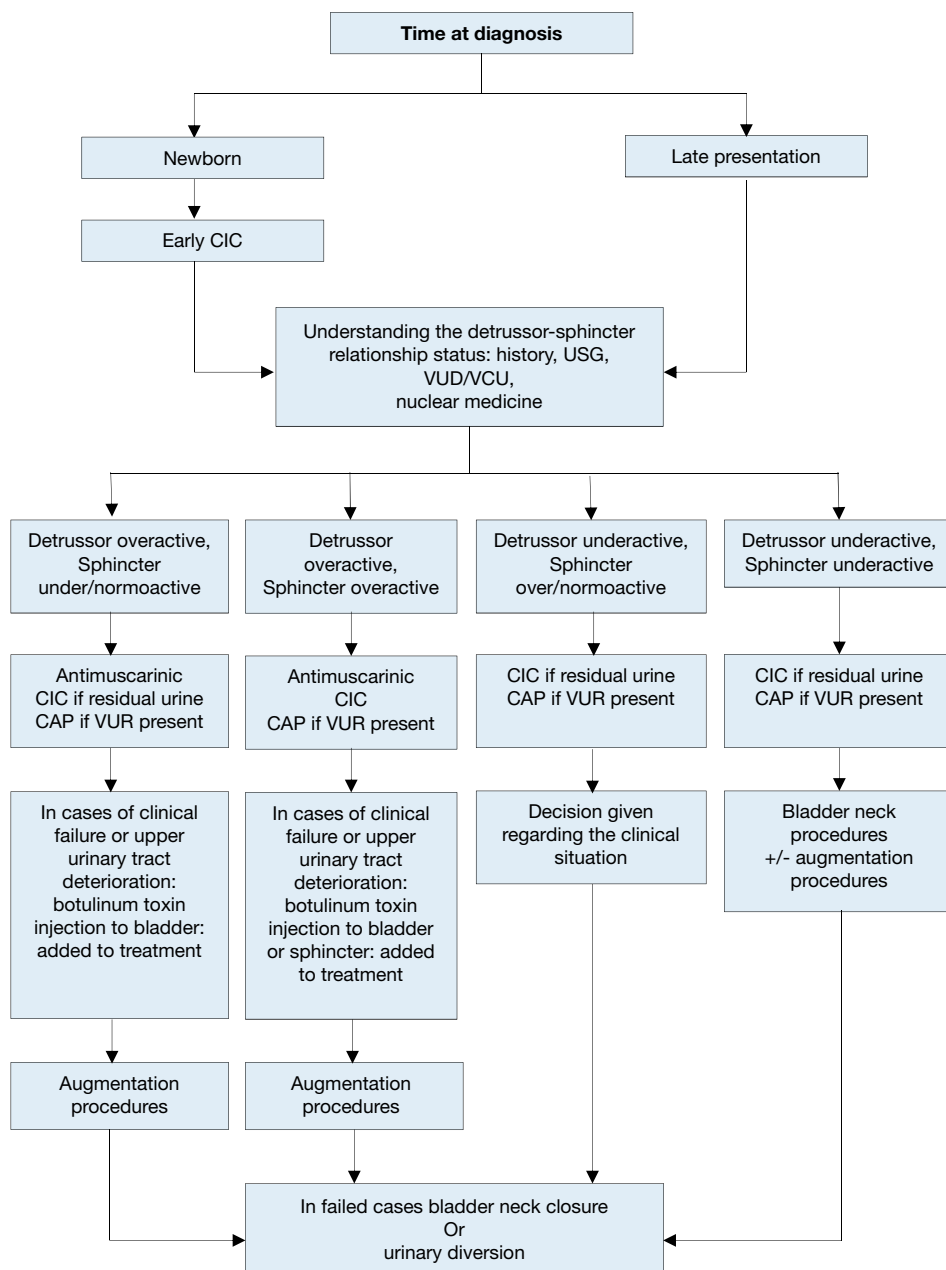
CAP = continuous anitbiotic prophylaxis; CIC = clean intermittent catheterisation; US = ultrasound; VCUG = voiding cystourethrography; VUD = videourodynamic; VUR = vesicoureteric reflux.

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 [411-413] (LE: 3; GR: B).

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. IC should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction [319, 411, 414-421] (LE: 2; GR: B). Babies without any clear sign of outlet

obstruction IC 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 [422, 423].

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 [388, 421, 424] (LE: 3). The retrospective evaluation of patients has also shown that significantly fewer augmentations were required in patients with an early start of IC [415, 420] (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 [424-431] (LE: 3; GR: B). 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 [432] (LE: 4; GR: C).

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 cmH$_2$O and bladder compliance was increased to at least 20 cmH$_2$O/mL. However, findings are limited by the lack of controlled trials and studies involving small patient numbers [373, 433-437]. 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 [438-443].

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 [373, 444-446].

Injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative (LE: 3; GR: C). 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 [447, 448].

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 [449].

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 [450-454] (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 [455]. Electrostimulation of the bowel may also offer a variable improvement in some patients [456] (LE: 3; GR: C).

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 clean IC, patients who

are asymptomatic do not need treatment [457-459] (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 [460, 461].

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 upper urinary tract 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 [462]. 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 [463, 464].

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. Alpha-adrenergic receptor stimulation of the bladder neck has not been very effective [465-470].

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% [471]. 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 [471].

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 [472-474].

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 upper urinary tract 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 [472].

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 [475-480]. In a study including 153 patients with a median follow-up time of 28 years [477], 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 is poor data on follow-up schemes; after a reasonable follow-up time (e.g. 10 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

LUTD = lower urinary tract dysfunction; NDSD = neurogenic detrusor-sphincter dysfunction; UTI = urinary tract infection; VUR = vesicoureteral reflux.

3.12 Dilatation of the upper urinary tract (UPJ and UVJ obstruction)

3.12.1 *Epidemiology, aetiology and pathophysiology*

Dilatation of the upper urinary tract 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 [481]. 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 [482].

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 [483].

3.12.2 *Diagnostic evaluation*

The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [484]. 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 [485].

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 [486]. 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) [487];
- urethral valves;
- ureteroceles;
- diverticula;
- neurogenic bladder.

Conventional VCUG is the method of choice for primary diagnostic procedures [488].

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 (^{99m}Tc) 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 [489]. Oral fluid intake is encouraged prior to the examination. At 15 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 [490]. 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 1 to 16 years, up to a maximum dose of 40 mg.

Figure 7: Diagnostic algorithm for dilatation of the upper urinary tract

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                          ┌─────────────────────┐
                          │     Postnatal US    │
                          └─────────────────────┘
                                    │
                ┌───────────────────┴───────────────────┐
     ┌──────────────────────────┐         ┌──────────────────────────┐
     │ Dilatation (uni- or      │         │      No dilatation        │
     │ bilateral)               │         │                           │
     └──────────────────────────┘         └──────────────────────────┘
                │                                      │
     ┌──────────────────────────┐         ┌──────────────────────────┐
     │ Voiding cystourethrogram │         │  Repeat US after 4 weeks  │
     │ (VCUG)*                  │         │                           │
     └──────────────────────────┘         └──────────────────────────┘
                │
                └──────────►┌──────────────────────────┐
                            │   Diuretic renography     │
                            └──────────────────────────┘
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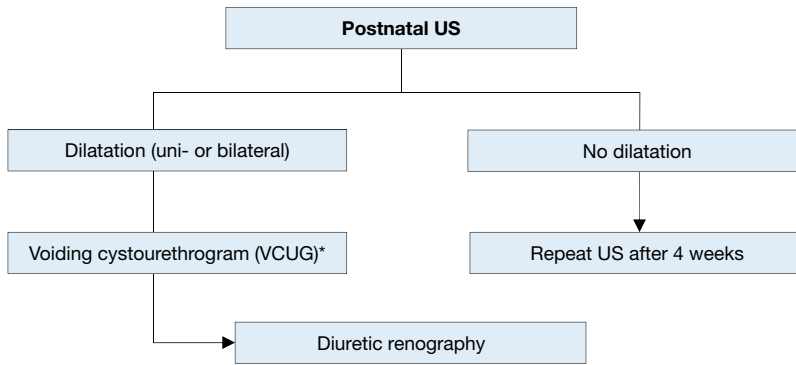
A diagnostic work-up including VCUG must be discussed with the parents, as it is possible that, even if reflux is detected, it may have absolutely no clinical impact. However, it should be borne in mind that reflux has been detected in up to 25% of cases of prenatally detected and postnatally confirmed hydronephrosis [487].
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 [491].

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 [492]. In experienced hands, laparoscopic or retroperitoneoscopic 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 [493].

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 [494, 495]. 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 [496]. Robotic-assisted laparoscopic pyeloplasty (RALP) has all the same advantages as of LP plus better maneuverability, improved vision, ease in suturing and increased ergonomics but higher costs [497, 498]. 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 [499]. 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 [500].

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 [501]. Data suggest that children with a ureteric diameter of > 10-15 mm are more likely to require intervention [502].

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 antireflux repair. Several tailoring techniques exist, such as ureteral imbrication or excisional tapering [503]. 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

Recommendations	LE	GR
Include serial US and subsequent diuretic renogram and sometimes VCUG in postnatal investigations.	2	B
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

UPJ = ureteropelvic junction; US = ultrasound; VCUG = voiding cystourethrography.

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 [504]. VUR 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% [505]. Among infants prenatally identified with hydronephrosis on US, who were screened for VUR, the prevalence was 16.2% (7-35%) [506]. 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%) [506].

However, reflux detected by sibling screening is associated with lower grades [506] and significantly earlier resolution [507]. 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 [508, 509].

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 [510-513].

There is a clear co-prevalence between LUTD and VUR [317]. LUTD 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 [317]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [514]. 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 OAB and 24% had voiding phase dysfunction [515].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy [507]. Faster resolution of VUR is more likely with age < 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 [516, 517].

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [518-520].

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 wellbeing [521-523].

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 [524-529], whereas in patients with LUTD, this may increase up to 30% [523, 530, 531]. 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 [532].

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 [533]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [534, 535] (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 [535].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [536]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [537-539]. 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 [535]

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

DMSA is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. DMSA is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, DMSA uptake is poor and appears as cold spots. DMSA 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 [535, 540]. DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [541]. Children with a normal DMSA scan during acute UTI have a low-risk of renal damage [541].

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) [317]. 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 [542, 543].

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 a rare entity, and if present it is likely to be low grade [524, 544]. 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 [506]. 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 [506]. DMSA 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 [506, 526, 545, 546]. When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [546]. 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 [506, 508, 547, 548]. 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
Inform parents of children with VUR that siblings and offspring have a high prevalence of VUR.
Use renal US for screening of sibling(s).
Use VCUG if there is evidence of renal scarring on US or a history of UTI.
Do not screen older toilet-trained children since there is no added value in screening for VUR.

US = ultrasound; UTI = urinary tract infection; VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.

3.13.2.4   Children with febrile urinary tract infections
A routine recommendation of VCUG at 0-2 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 [549]. 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 [311, 550-552].

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 [515, 553]. The coexistence 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 coexistence 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 [554].
*   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 [330, 553, 555-557].
*   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 [558].

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 (VUR) 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 [330, 559-561]. Trials show benefit of CAP is none or minimal in low-grade reflux. Continuous anitbiotic 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 [341-344, 562, 563]. 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 [564-567].

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) [568, 569].

Although the best results have been obtained with PTFE [570], due to concerns about particle migration, PTFE has not been approved for use in children [571]. 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 [572]. 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 [559].

In a meta-analysis [573] 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%) [574]. 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%) [575].

The most popular and reliable open procedure is cross trigonal reimplantation 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 reimplantation (Politano-Leadbetter technique) and infrahiatal reimplantation (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 [576]. 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, 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 [577, 578].

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 [558, 577, 579-586].

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 1-5 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 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 : • 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, multidisciplinary approach is needed.	A

LUTD = lower urinary tract dysfunction; UTI = urinary tract infection.

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 highgrade 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 certain circumstances (e.g. oxalosis or nephrocalcinosis).

Paediatric stone disease has its own unique features, which are different in both presentation and treatment compared to stone disease in adults. In contrast to adults with stone disease who are more likely to be male, boys and girls are affected almost equally. Most paediatric stones are located in the UUT. 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 [587]. Patients with augmented bladder constitute another important group with a risk up to 15% [588].

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 [589, 590] especially in girls, Caucasian ethnicity, and older children [591]. More than 70% of stones in children contain calcium oxalate, while infection stones are found more frequently in younger children [592].

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. Supersaturation 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 [593].

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 with a normal serum calcium level. Secondary hypercalciuria occurs when a known process produces excessive urinary calcium. In secondary (hypercalcaemic) hypercalciuria, a high serum calcium level may be due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilisation, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) [594].

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 [593, 594]. 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 criterion standard 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. Further evaluation includes levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, magnesium, pH, and parathyroid hormone if hypercalcemia is detected. Freshly voided urine should be measured for pH [593-596]. A 24-hour urine collection should also be made to measure calcium, phosphorus, sodium, magnesium, 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 [597]. A brief trial of a low-calcium diet can be carried out to determine if exogenous calcium intake is contributing to high urinary calcium. However, great caution should be used when trying to restrict calcium intake for long periods (LE: 3; GR: B).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat idiopathic hypercalciuria at a starting dosage of 0.5-1 mg/kg/day, in case of sustaining hypercalciuria up to 2 mg/kg/day [598-601] (LE: 3; GR: C). 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 [598, 602] (LE: 4; GR: C).

Hyperoxaluria: Oxalic acid is a metabolite excreted by the kidneys. Only 10-15% of oxalate comes from diet. The average child excretes less than 50 mg (0.57 mmol)/1.73 m^2/day [598, 603], 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 primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. In primary hyperoxaluria there is increased deposition of calcium oxalate in the kidney and in urine. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue in resulting deposition of calcium oxalate in other tissues. 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 who have high levels of oxalate excretion in urine may not have any documented metabolic problem or any dietary cause. This is known as idiopathic 'mild' 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 [598, 603] (LE: 4; GR: C).

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 [604, 605].

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 [606, 607].

Due to the increased stone risk in hypocitraturia, the restoration of normal citrate levels is advocated to reduce stone formation. Although some studies have shown that citrate replacement therapy reduces the risk of stone formation in an adult population, 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 [605] (LE: 3; GR: B). 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 [598].

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 [598]. In cases who failed with conservative measures with sustaining hyperuricosuria, 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 shock wave 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. If this treatment fails, the use of alphamercaptopropionyl glycine may 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 [608] (LE: 4; GR: C).

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 [609] and in non-endemic regions [592, 610]. 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 [611, 612].

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 [613-615] (LE: 2; GR: B). 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 [616]. 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 [587, 617, 618].
Metabolic evaluation includes:
* Family and patient history of metabolic problems;
* 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


```
                        Paediatric stone patient
                                 │
            Elimination of stones by spontaneous passage
                 or active removal (SWL, surgery)
                                 │
                           Stone analysis
        ┌────────────────┬──────────┴──────────┬──────────────────┐
  Mg Ammonium        Uric acid stone        Cystine          Calcium stones
   phosphate                                                    CaOX-CaPO
   (struvite)
        │                   │                   │
  urine culture       urine pH            urine pH
                      urine and serum     urine cystine
                      uric acid levels    level
        │                   │                   │
   possibly                                  cystinuria
 urease producing          │                   │
   bacteria           acidic urine      High fluid intake
        │             hyperuricosuria    potassium citrate
  Total elimination   hyperuricemia      3-4 mEq/kg/d
   of stone                │             mercaptopropiyonilglycine
  (surgery/SWL)      Alkali replacement – 10-15 mg/kg/d
   antibiotics         K citrate
                     Allopurinol (10 mg/kg)
                      low purine diet
```

```
                                    urine - blood pH
  serum PTH — hypercalcaemia — urine - blood Ca - uric acid levels, Mg, Phosphate
                                urine Ca-Oxalate-Citrate-Mg-Uric A -Phosphate
                         │                                │
                   urine pH < 5.5                   urine pH > 5.5
                         │                                │
              Hyperparathyroidism           Further investigation for RTA
        ┌──────────────┬──────────────┬──────────────┐
  hypercalciuria   hyperoxaluria  hyperuricosuria  hypocitraturia
        │              │               │               │
   K-citrate      Regular calcium    Alkali          Citrate
    diet             intake         replacement     replacement
 (normal calcium  Diet low in ox.   (K-citrate)      K-citrate
  low sodium        K-citrate       allopurinol
   intake)          pyridoxine
  HCTZ (diuretic)
```

Ca = calcium; HCTZ = hydrochlorothiazide; Mg = magnesium; Ox = axalate; 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 [617, 619, 620].
Adult literature reveals the benefits of medical expulsive therapy (MET). Although, experience in children is limited, 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 [621].

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 [622, 623].

3.14.4.1 Extracorporeal shock wave lithotripsy

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney [624-631].

The mean number of shock waves for each treatment is approximately 1800 and 2000 (up to 4000 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 [619, 632, 633]. 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 [634] (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 [619, 632, 633, 635-639].

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% [640-643].

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 [640-642, 644, 645].

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 [638].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient [637, 638]. 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 [618, 639].

The Hounsefield 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 [623] and 1000 [646]. Two recent 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 [647, 648].

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 [649]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PCNL).

3.14.4.2 Percutaneous nephrolithotomy

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery can 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 [649, 650].

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 [651-656].

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% [657-662] and is closely associated with stone burden, operative time, sheath size and the number of tracts [657, 663, 664]. In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% [657-659, 661, 662, 665] and the origin of fever is not always found to be the infection. With the availability of smaller size instruments, miniaturised PCNL ('mini-perc') through a 13F or 14F sheath [650, 666, 667] as well as ultramini-PCNL (UMP) through 12F sheaths [668] have become possible, with decreased transfusion rates [666]. 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 [669]. 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 [670] (LE: 3, GR: B). For stones 10-20 mm, micro-PNL was shown to have comparable results, with lesser bleeding, compared to mini-PCNL [671] (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 [660, 665] or totally tubeless [672].

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).

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 [649, 673-679] (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 [652, 676, 678, 680-686].

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). 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 [687].

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 [688-692]. 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 [689, 690]. 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 [688, 690-693]. The need for additional procedures was related to stone size [692]. A comparative study showed that retrograde intrarenal surgery (RIRS) had similar stone-free rate compared to ESWL after three months, with fewer sessions [209] (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 [694-696].

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. 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	Endocopic	2b	B		Open is easier and with less operative time with large stones.

Cystine and uric acid stones excluded.

PCNL = percutaneous nephrolithostomy; SWL = shock-wave 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.	3
Open surgery for stone disease in children is an exceedingly rare requirement. Contemporary surgical treatment is based on minimally invasive modalities. Open surgery is indicated under circumstances in which the child is very young with large stones in association with congenital problem requiring surgical correction and/or with severe orthopedic deformities that limit positioning for endoscopic procedures.	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
In most cases, plain abdominal X-ray and US are sufficient for diagnosis and follow-up.	2b	B
Use non-contrast 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
Use appropriately-sized instruments in order to decrease the number of complications during surgical treatment.	2b	B

CT = computed tomography; US = ultrasound.

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 [697].

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 [698]. 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 [699].

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 [700-702]. 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 [703, 704]. Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [705].

In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional [706, 707]. The corresponding ureter is a megaureter. 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 seen 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 [708]:
- 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 [708]:
- 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 [709, 710]. 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 [711-713]. 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 [714]. Based on the prevalence of high-grade reflux, VCUG is mandatory for identifying ipsilateral or contralateral reflux, and assessing the degree of intraurethral prolapse of the ureterocele [715]. Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic megaureter.

3.15.3.2 Ectopic ureter

Most of the ectopic megaureters 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 [716].
- 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 [717]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele [718, 719].

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 [720]. Filling the bladder with methylene blue and checking for clear urine output from the vagina can give clear evidence of extrasphincteric 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
The management is controversial with a choice between a non-operative approach, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, or complete primary reconstruction [721-726]. 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 [727]. 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, without severe hydroureteronephrosis of the ureterocele moiety or high-grade (over grade III) reflux [727, 728].
         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 [699]. 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 [729].
         Surgery may vary from upper pole nephrectomy to complete unilateral LUT reconstruction [705, 725, 730-733]. In an ectopic ureterocele with severe hydroureteronephrosis and without reflux, the primary upper tract approach without endoscopic decompression (partial upper-pole nephroureterectomy, pyelo/ureteropyelo/ureterostomy and upper-pole ureterectomy) gives up to an 80% chance of being the definitive treatment [727, 734].

Figure 9: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life
         [727]
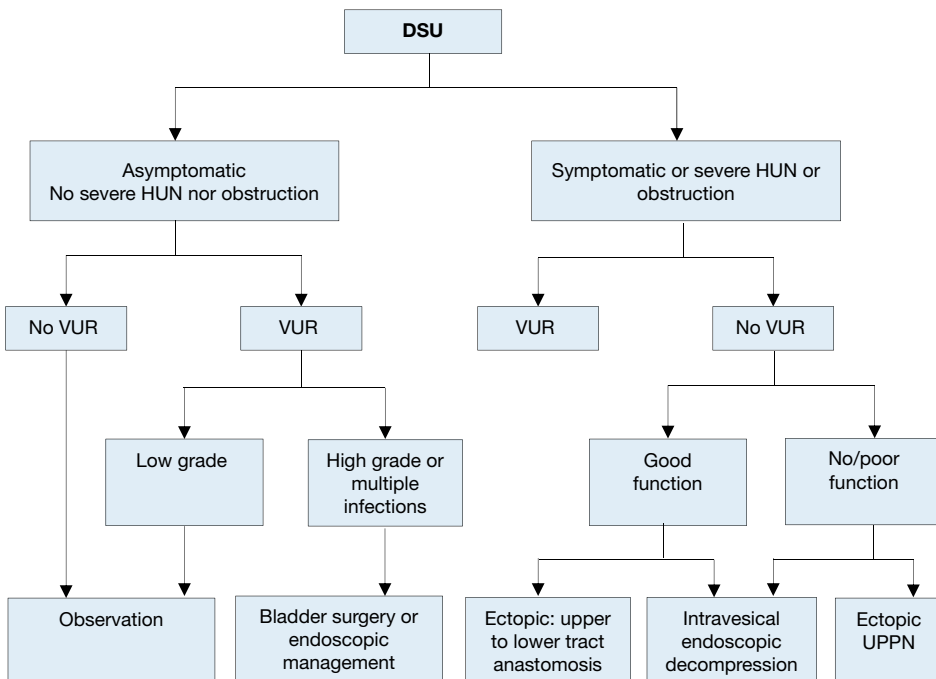
DSU = duplex system ureterocele; HUN = hydroureteronephrosis; UPPN = upper pole partial nephrectomy; VUR = vesicoureteric reflux to the lower pole.

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 reimplantation/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 [735-737]. In patients with bilateral single ectopic ureters (a very rare condition), an individual approach depending on the sex, renal and bladder function is necessary. Usually the bladder neck is insufficient in these patients [738-741].

*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: • 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 US, radionuclide studies (MAG3/DMSA), VCUG, magnetic resonance urography, high-resolution 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.		

DMSA = dimercaptosuccinic acid; MRI = magnetic resonance imaging; US = ultrasound; VCUG = voiding cystourethrography.

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) [742, 743].

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 pejorative 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, 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 added 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 for the published literature on DSD. There are no RCTs and most studies are based on retrospective clinical descriptive studies (LE: 4) or are expert opinion. An exception is the risk of gonadal cancer, for which the LE is higher.

DSD 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 [744, 745].

The diagnosis and treatment of DSD requires a multidisciplinary 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 new 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 [742, 743, 746].
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 [742]. 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 1 year [743].

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 [747-750] (LE: 2; GR: B). In the presence of androgen insensitivity, good outcome of sexual function is questioned and gender conversion can be considered [751-753].

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 = adrenocorticotropic 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
• Clinical examination
• Ultrasound
• Genitography
• Cystoscopy
• Diagnostic laparoscopy
Therapeutic role
• 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 an accurate description of the ambiguous genitalia, some 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 [754].

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 Mülllerian structures can be evaluated. Is there a vagina? Are there some abdominal gonads? Is there a vaginal or utriculur structure visible [755, 756]?

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 [757, 758].

3.16.3   Management
Referring to the consensus document [742, 743], 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 [759].

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 [760].

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 [761, 762]. Informed parental consent should be obtained. Although some techniques that conserve erectile tissue have been described, the long-term outcome is unknown [763].

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 [764, 765].

Vaginoplasty should be performed during the teenage years. Every technique (self-dilatation, skin or bowel substitution) has its specific advantages and disadvantages [766]. 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. The 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 [767] (GR: A).

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 multidisciplinary 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 multidisciplinary 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 [768-770]. PUV are found in 1 in 1,250 in a population undergoing foetal US screening [484]. An incidence of PUV of 1 in 5,000-12,500 live-births has been estimated [771, 772]. In one report, up to 46% of foetuses with a PUV diagnosis were terminated, indicating a possible decrease in incidence [773].

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) [774], the original classification by Hugh Hampton Young remains the most commonly used [775].

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' [775].

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' [775].

The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane [776]. The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca [777].

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 upper urinary tracts. 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 hydroureteronephrosis 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 ($p = 0.27$) [778]. 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 (VCUG) 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 [779]. 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 [780]. Other types of pop-off mechanism include bladder diverticula and urinary extravasation, with or without urinary ascites [781]. However, in the long-term, a supposed protective effect did not show a significant difference compared to other patients with PUV [782, 783].

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 µmol/L is correlated with a better prognosis [770]. Initial management includes a multidisciplinary team involving a paediatric nephrologist.

3.17.4   *Management*
3.17.4.1   *Antenatal treatment*
About 40-60% of PUV are discovered before birth [784]. 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 < 90mmol/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 [785].

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% [785-787]. Although shunting is effective in reversing oligohydramnios, it makes no difference to the outcome and long-term results of patients with PUV [786, 787]. The PLUTO-trail (randomised study) could not prove a benefit of placing a shunt [788].

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 [789, 790].

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 were 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 studied demonstrated a significant lower urethral stricture rate using the cold knife compared to diathermy [791]. 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 [792].

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 upper urinary tracts in over 90% of cases [793]. 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 [794, 795].

High diversion. If bladder drainage is insufficient to drain the upper urinary tract, 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 [796-798]. 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% [799]. During the first months of life, antibiotic prophylaxis may be given especially in those with high-grade reflux [562] and in those with a phimosis, circumcision can be discussed in order to reduce the risk of UTIs [800]. 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 [768, 801]. 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 [802].

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 [770, 779]. 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) [803, 804]. 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 post-void residual [PVR] was reduced from 16 to 2 mL) [805] and in another study tamsulosin was effective [806]. Between 10% and 47% of patients may develop end-stage renal failure [768-770]. High creatinine nadir and severe bladder dysfunction are risk factors for renal replacement therapy [807]. Renal transplantation in these patients can be performed safely and effectively [808, 809]. Deterioration of the graft function is mainly related to LUTD [809, 810]. 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
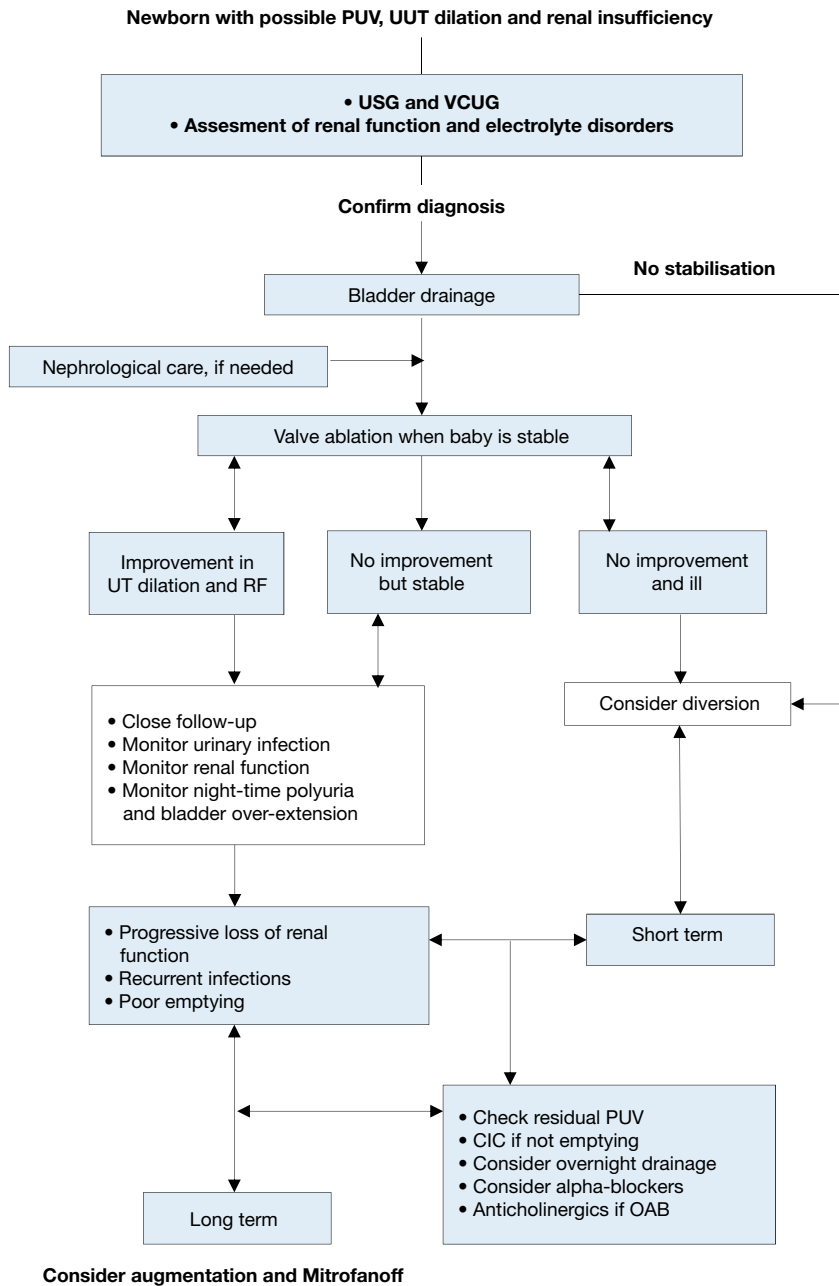
CIC = clean intermittent catheterisation; OAB = overactive bladder; PUV = posterior urethral valve;
RF = renal function; UT = urinary tract; UUT = upper urinary tract; VCUG = voiding cystourethrogram.

3.17.6   Summary
Posterior urethral valves (PUV) 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 hydroureteronephrosis 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 µmol/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 upper urinary tract, 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
PUV 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 deteroration because of bladder dysfunction.	2a
Renal transplantation in these patients is safe and effective, if the bladder function is normalised.	

Recommendations	LE	GR
Diagnose PUV initially by US but a VCUG is required to confirm the diagnosis. Assess split renal function by DMSA scan or 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 suprapupic diversion for bladder drainage in case 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 life long, in all patients.	3	B

DMSA = dimercaptosuccinic acid scan; MAG3 = mercaptoacetyltriglycine; US = ultrasound; VCUG = voiding cystourethrogram.

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 [811]. In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract [812]. 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 [811].

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 perirenal fat, much weaker abdominal muscles, and a less ossified and therefore much more elastic and compressible thoracic cage [813].

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) [814].

Table 13: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [814]

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 [815].
　　　　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 [816]. 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 [817].
　　　　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
　　　　CT 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 [818].
　　　　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 IVP 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 [819].

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 CT scanning for diagnostic and staging purposes.	B
Mnanage most injured kidneys conservatively.	B
Offer surgical intervention in case of haemodynamic instability and a Grade V renal injury.	A

CT = computed tomography.

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 [820]. 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 [820]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to ten minutes after injection of the contrast material [821]. 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 nephrostromy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries [822].

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 [823].

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 CT.	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

CT = computed tomography.

*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 [824].

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 [825].
        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 [826].

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.

Intraperitoneal 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 Intraperitoneal injuries
The accepted management of intraperitoneal 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 [827]. Usually, after about seven to ten days, a repeat cystogram is performed to ensure healing is taking place properly.

3.18.3.2.2 Extraperitoneal injuries
Non-operative management with catheter drainage for seven to ten days alone is the method of choice for extraperitoneal 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 [828].

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 full to its capacity and an additional film is taken after drainage.	A
Manage extraperitoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	A
Do not delay treatment of intraperitoneal 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 [829].

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-threateninginjuries.

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 [830].

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 [831]. 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% [832]. 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% [833]. Another study reported strictures and impotence in 67% of boys, although all the boys were continent [832].

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 14 children undergoing this procedure, this resulted in a stricture rate of 29% and incontinence in 7% of patients [834].

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: • 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 [835]. 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 [836]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [837].

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 [838, 839].

Table 14: Pre-operative fasting times for elective surgery

Ingested material	Minimum fasting period (h)
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 [840]. 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 [841].

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 [841].

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) [842]. Calculations have shown that anaesthetised and non-anaesthetised children have similar fluid requirements [843].

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 [844].

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 [845]. Berry (1986) proposed simplified guidelines for fluid administration according to the child's age and severity of surgical trauma [846] (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, *et al.* [845]			
Hour of fluid replacement	**Maintenance fluid**	**Fasting deficit replacement**	**Persistent losses**
First hour		50%	Third space + blood loss replacement
Second hour	As Table 14	25%	
Third hour		25%	
Berry [846]			
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 [841].

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) [839].

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 [835, 844]. Intra-operative administration of glucose-free isotonic hydrating solutions should be the routine practice for most procedures in children over 4-5 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 [839].

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 [836], while remembering that withholding oral fluids post-operatively from children undergoing day surgery helps prevent vomiting [847]. 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 [848]. Berry's fluid replacement guidelines can be followed, provided the child is given lactated Ringer's solution or polyionique B66, which has an osmolarity similar to plasma [849].

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 h (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 5 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 [849, 850]. 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 [839, 849, 851-854]. 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 [839].

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention, especially the risk of polyuria due to 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% [847, 855, 856]. 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 [857]. 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 [858]. 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 [859]. 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

Table 17: List of several drugs used in post-operative pain management in children [864, 871, 875, 883-885]

Name	Route of administration	Dose	Side effects	General remarks	Caution
Non-narcotics					
Acetaminophen	Rectal Oral Intravenous	40 mg/kg loading, 20 mg/kg/dose 4 times/day 15-40 mg/kg, followed by 30 mg/kg/8 h Propacetamol (prodrug)	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
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, dipyrone	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			Nausea, vomiting, dyspepsia, constipation, urinary retention, respiratory depression, drowsiness, euphoria		
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, 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

Drug	Route	Dose			
Codeine	Oral	1 mg/kg, single dose	Respiratory depression not seen after single dose	Both antitussive and analgesic effect	
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	IM injection not recommended < 2 months old: be careful
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 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 [860]. However, there is still no standardised algorithm for management of post-operative pain in children [861]. 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 [862].

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 [863-867]. Many studies have indicated that deficient or insufficient analgesia may be the cause of future behavioural and somatic sequelae [868-871]. 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 [872, 873].

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 [874-879].

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 [880]. 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 [876]. 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 [881]. 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 [882]. 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 [886]. Despite this, adequate pain management is still below expectation [887]. 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 [888-892].

Although DPNB and topical anaesthetics seem to have a similar post-operative analgesic effect, DPNB is still the most preferred method [893] (LE: 1a). Ultrasound guidance may improve the results, with an increase in procedural time [894, 895]. 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 [896-901].

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 [902-916]. Both single and combined use of these agents is effective [903, 904, 906, 907, 912, 914].

Penile blocks can be used for post-operative analgesia and have similar post-operative analgesic properties as caudal blocks [917]. Two penile blocks at the beginning and end of surgery seems to provide better pain relief [918]. 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 [356, 919-921] nerve block [922, 923], wound infiltration or instillation, and irrigation with local anaesthetics [924-926] have been shown to have adequate post-operative analgesic properties. Combinations may improve the results [927].

3.20.3.4 Bladder and kidney surgery

Continuous epidural infusion of local anaesthetics [928-930], as well as systemic (intravenous) application of analgesics [931], 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 [920, 932-935].

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 [936].

Caudal blocks plus systemic analgesics [937], and continuous epidural analgesia, are effective in terms of decreased post-operative morphine requirement after renal surgery [938, 939]. However, when there is a relative contraindication to line insertion, a less experienced anaesthetist is available, or parents prefer it [940], 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 [941]. For laparoscopic approaches, intraperitoneal spraying of local anaesthetic before incision of the perirenal fascia may be beneficial [942].

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	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 (IV PCA)
Severe (upper abdominal or lombotomy)			Epidural local/major peripheral nerve/ plexus block/opioid injection (IV PCA)

IV PCA = intravenous patient-controlled analgesia; NSAID = non-steroidal anti-inflammatory drugs.

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

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5.   CONFLICT OF INTEREST

EAU Guidelines on Urological Trauma

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**European
Association
of Urology**

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1. INTRODUCTION

1.1 Aim and objectives
The European Association of Urology (EAU) Guidelines Group for Urological Trauma 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.

1.2 Panel composition
The EAU Urological Trauma Guidelines Panel consists of an international group of clinicians with particular expertise in this area, The panel includes urologists and an interventional radiologist.
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.

1.2.1 Acknowledgement
The EAU Urological Trauma Guidelines Panel gratefully acknowledge the support of Dr. P. Macek, who contributed as a Guidelines Associate to the ongoing systematic review on: Is conservative/minimally-invasive management of Grade 4-5 renal trauma safe and effective compared with open surgical exploration.

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. Also a number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal are available [2-5]. All documents can be viewed free access through the EAU website: http://uroweb.org/guideline/urological-trauma/?type=appendices-publications.

1.4 Publication history
The Urological Trauma Guidelines were first published in 2003. This 2016 document presents a limited update of the 2015 publication. The literature was assessed for all chapters.

1.4.1 Summary of changes
The literature for the complete document has been assessed and updated, wherever relevant.
Key changes for the 2016 publication:
- 4.1 Renal Trauma section – the imaging sections (4.1.2.3 Imaging: criteria for radiographic assessment, 4.1.2.3.1 Ultrasonography and 4.1.3.1.3 Interventional radiology have been updated). As a result, Figures 4.1.1 Evaluation of penetrating renal trauma in adults and 4.1.2 Evaluation of penetrating renal trauma in adults, have been adapted.

2. METHODS

2.1 Evidence sources
The Urological Trauma guidelines are based on a review of the relevant literature, using the following databases: Medline, Embase, Cochrane, and other source documents published between 2002 and 2014. A critical assessment of the findings was made. The majority of publications on the subject are comprised of case reports and retrospective case series. The lack of high-powered randomised controlled trials makes it difficult to draw meaningful conclusions. The panel recognises this critical limitation.

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]. 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 2015 Urological Trauma Guidelines were subjected to peer review prior to publication.

2.3 Future goals
The Urological Trauma Guidelines Panel aim to systematically address the following key clinical topics in future updates of the Guidelines:

- Is conservative/minimally-invasive management of Grade 4-5 renal trauma safe and effective compared with open surgical exploration?
- What are the comparative outcomes of early endoscopic realignment versus suprapubic diversion alone for pelvic fracture related urethral injuries? [7]
- What are the comparative risks and benefits of conservative versus surgical management of extraperitoneal bladder injury?
- What is the management of radiation therapy-induced toxicity to the urogenital tract?

These reviews will be performed using standard Cochrane systematic review methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

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 5 million deaths each year worldwide and causes disability to millions more [8, 9].

About half of all deaths due to trauma are in people aged 15-45 years and in this age group it is the leading cause of death [10]. Death from injury is twice as common in males as in females, especially from 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 [11].

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 [12, 13], and in 10% of all abdominal trauma cases [14]. 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 [15].

Ureteral trauma is relatively rare and mainly due to iatrogenic injuries or penetrating gunshot wounds, both in military and civilian settings [16].

Traumatic bladder injuries are usually due to blunt causes (MVA) and associated with pelvic fracture [17], 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 [18].

Genital trauma is much more common in males due to anatomical considerations and more frequent participation in physical sports, violence and war-fighting. Of all genito-urinary injuries, $^1/_3$-$^2/_3$ involve the external genitalia [19].

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 motor vehicle collisions, falls, and other domestic accidents). Intentional trauma accounts for approximately half of the trauma-related

deaths worldwide [9]. A specific type of unintentional injury consists of 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 then 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 track of the projectile.

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 [20]. 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 were omitted from these guidelines.

3.3 Initial evaluation and treatment

The initial emergency assessment of the 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 [21, 22]. 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 [23]. In any penetrating trauma, tetanus vaccination should be considered according to the patient's vaccination history and the features of the wound itself (Centers for Disease Control and Prevention [CDC] tetanus wound management) [24].

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 [13, 25]. Renal injuries are associated with young age and male gender, and the incidence is about 4.9 per 100,000 [26]. Most injuries can be managed conservatively as advances in imaging and treatment strategies have decreased the need for surgical intervention and increased organ preservation [14, 27, 28].

4.1.1.2 Mode of injury

4.1.1.2.1 Blunt renal injuries

Blunt mechanisms include motor vehicle collision, falls, vehicle-associated pedestrian accidents and assault [29]. 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%) [14] 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 as high as 20% or higher [30, 31]. Bullets have the potential for greater parenchymal destruction and are most often associated with multiple-organ injuries [32]. 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 [20] (Table 4.1.1). This validated system has clinical relevance and helps to predict the need for intervention [15, 33, 34]. It also predicts morbidity after blunt or penetrating injury and mortality after blunt injury [15].

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 *or* Vascular: segmental renal artery or vein injury with contained haematoma, or partial vessel laceration, or vessel thrombosis
5	Laceration: shattered kidney *or* Vascular: renal pedicle or avulsion

Advance one grade for bilateral injuries up to grade III.

Proposals for changes to the AAST classification include a substratification 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 [35], as well as a suggestion that grade 4 injuries comprise all collecting system injuries, including ureteropelvic junction (UPJ) injury of any severity and segmental arterial and venous injuries, while grade 5 injuries should include only hilar injuries, including thrombotic events [36].

*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 [37]. In patients with a solitary kidney, the whole functioning renal mass may be endangered [38, 39]. Since pre-existing abnormality makes injury more likely following trauma, hydronephrosis due to UPJ abnormality, calculi, cysts and tumours may complicate a minor injury [39].

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	GR
Assess haemodynamic stability upon admission.	A*
Obtain a history from conscious patients, witnesses and rescue team personnel with regard to the time and setting of the incident.	A*
Record past renal surgery, and known pre-existing renal abnormalities (UPJ obstruction, large cysts, lithiasis).	A*
Perform a thorough physical examination to rule out penetrating injury. Flank pain, flank abrasions and bruising ecchymoses, fractured ribs, abdominal tenderness, distension or mass, could indicate possible renal involvement.	A*

Upgraded following panel consensus.
UPJ = ureteropelvic junction.

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 [40].

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 [41, 42]. Haematuria that is out of proportion to the history of trauma may suggest pre-existing pathology [43]. A urine dipstick is an acceptable, reliable and rapid test to evaluate haematuria, however, the rate of false-negative results range from 3-10% [44].

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	GR
Test for haematuria in a pt with suspected renal injury (visually and by dipstick).	A*
Measure creatinine level to identify patients with impaired renal function prior to injury.	C

Upgraded following 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 macroscopic haematuria or microscopic haematuria and hypotension (systolic blood pressure < 90 mmHg) [29, 45-48]. 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 presence or absence of haematuria [29, 45-48].

In patients with penetrating trauma, with the suspicion of renal injury, imaging is indicated regardless of haematuria [29, 45-48].

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 [49-51] and the American College of Radiologists (ACR) Renal Trauma guidelines considers US usually not appropriate in renal trauma [46].

The use of contrast enhanced US (CEUS) with microbubbles increases the sensitivity of US to solid organ injury [52]. 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 CT in the follow-up of renal trauma [53-55].

4.1.2.3.2 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 [46].

4.1.2.3.3 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 preoperative imaging [56]. The technique consists of a bolus intravenous injection of 2 mL/kg of radiographic contrast followed by a single plain film taken after 10 minutes.

4.1.2.3.4 Computed tomography (CT)
Computed tomography is the imaging modality of choice in haemodynamically stable patients following blunt or penetrating trauma. CT 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.

4.1.2.3.5 Magnetic resonance imaging (MRI)
The diagnostic accuracy of MRI in renal trauma is similar to that of CT [62, 63]. 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 MRI impractical.

4.1.2.3.6 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 [64]. 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 [65]. 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 [66-68].

Most patients with grade 4 and 5 injuries present with major associated injuries, and consequently often undergo exploration and nephrectomy rates [69], although emerging data indicate that many of these patients can be managed safely with an expectant approach [70]. An initially conservative approach is feasible in stable patients with devitalised fragments [71], although these injuries are associated with an increased rate of complications and late surgery [72]. Patients diagnosed with urinary extravasation from solitary injuries can be managed without major intervention with a resolution rate of > 90% [70, 73]. 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 of repair are usually unsuccessful [74].

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 [75]. Selective non-operative management of abdominal stab wounds is generally accepted following complete staging in stable patients [68, 76]. 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 [77]. 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 [78].

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 [79]. Minor low-velocity gunshot and stab wounds may be managed conservatively with an acceptably good outcome [80]. 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 [81-83].

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 [84-86]. Currently there are no validated criteria to identify patients who require angioembolisation and the use of angioembolisation in renal trauma remains heterogeneous. Generally accepted CT findings indicating angioembolisation are active extravasation of contrast, arteriovenous fistula and pseudoaneurysm [87]. The presence of both active extravasation of contrast and a large haematoma ($\geq$ 25 mm depth) predict the need for angioembolisation with good accuracy [87, 88].

Angioembolisation has been utilised in the non-operative management of all grades of renal injury, however it is likely to most beneficial in the setting of high grade renal trauma (AAST $\geq$ 3) [84-86]. 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 [84, 85]. Increasing grade of renal injury is associated with increased risk of failed angioembolisation and need for repeat intervention [89]. Repeat embolisation prevents nephrectomy in 67% of patients and open surgery after failed embolisation usually results in nephrectomy [89, 90]. 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 [91]. 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 3 times more likely to fail in penetrating trauma [75] however, angioembolisation has been used successfully to treat arteriovenous fistulae and psuedoaneurysms in the non-operative management of penetrating renal trauma [92]. With studies reporting successful non-operative management of penetrating renal trauma, angioembolisation must be critically considered in this setting [92, 93].

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 [94]. However, management of renal injury may also be influenced by the decision to explore or observe associated abdominal injuries [95].

Continuing haemodynamic instability and unresponsive to aggressive resuscitation due to renal haemorrhage is an indication for exploration, irrespective of the mode of injury [75, 96]. 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 endourological techniques. Inconclusive imaging and a pre-existing abnormality or an incidentally diagnosed tumour may require surgery even after minor renal injury [43].

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 [97-100]. 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 [35].

4.1.3.2.2   Operative findings and reconstruction

The overall exploration rate for blunt trauma is less than 10% [96], and may be even lower as the conservative approach is increasingly adopted [101]. The goals of exploration following renal trauma are control of haemorrhage and renal salvage.

Most series suggest the transperitoneal approach for surgery [102, 103]. 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 [104]. 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 [105].

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; packing the fossa tightly with laparotomy pads temporarily can salvage the kidney [106]. 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 next 48 to 72 hours, CT scans can identify injuries and select patients for reconstruction or continued expectant management [107]. Ureteral stenting or nephrostomy diversion should be considered after delayed reconstruction due to the increased risk of post-operative urinary extravasation.

Renal reconstruction is feasible in most cases. The overall rate of patients who undergo a nephrectomy during exploration is around 13%, usually in patients with penetrating injuries and higher rates of transfusion requirements, haemodynamic instability, and higher injury severity scores [108]. Other intraabdominal injuries also slightly increase the need for nephrectomy [109]. Mortality is associated with overall severity of the injury and not often a consequence of the renal injury itself [110]. In gunshot injuries caused by a high-velocity bullet, reconstruction can be difficult and nephrectomy is often required [111]. 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 [112]. The use of haemostatic agents and sealants in reconstruction can be helpful [113]. In all cases, drainage of the ipsilateral retroperitoneum is recommended. Following blunt trauma, repair of vascular injuries (grade 5) is seldom, if ever, effective [114]. Repair should be attempted in patients with a solitary kidney or bilateral injuries [115], but is not used in the presence of a functioning contralateral kidney [28]. 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 conservative management

Recommendations	GR
Following blunt renal trauma, manage stable patients conservatively with close monitoring of vital signs.	B
Manage isolated grade 1-3 stab and low-velocity gunshot wounds in stable patients, expectantly.	B
Indications for renal exploration include: • haemodynamic instability; • exploration for associated injuries; • expanding or pulsatile peri-renal haematoma identified during laparotomy; • grade 5 vascular injury.	B
Treat patients with active bleeding from renal injury, but without other indications for immediate abdominal operation, with angio-embolisation.	B
Attempt renal reconstruction if haemorrhage is controlled and there is sufficient viable renal parenchyma.	B

4.1.4   *Follow-up*

The risk of complications in patients who have been treated conservatively increases with injury grade. Repeat imaging two-four days after trauma minimises the risk of missed complications, especially in grade 3-5 blunt injuries [116]. The usefulness of frequent CT scanning after injury has never been satisfactorily proved. 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 [117].

Nuclear scans are useful for documenting and tracking functional recovery following renal reconstruction [118]. Follow-up should involve physical examination, urinalysis, individualised radiological investigation, serial blood pressure measurement and serum determination of renal function [71]. A decline in renal function correlates directly with injury grade; this is independent of the mechanism of injury and the method of management [119, 120]. 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 [121]. In general, the literature is inadequate on the subject of 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 [122]. 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 [96].

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% [123, 124]. 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 [125].

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 [126]. Persistent urinary extravasation from an otherwise viable kidney after blunt trauma often responds to stent placement and/or percutaneous drainage as necessary [127].

Arteriovenous fistulae (AVF) 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 [128]. Post-procedural complications include infection, sepsis, urinary fistula, and renal infarction [129]. 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 [130]. Acute renal colic from a retained missile has been reported, and can be managed endoscopically if possible [131].

4.1.4.2 Recommendations for follow-up

Recommendations	GR
Repeat imaging in case of fever, flank pain, or falling haematocrit.	B
Follow-up approximately three months after major renal injury with hospitalisation. Include in each follow-up: physical examination, urinalysis, individualised radiological investigation, including nuclear scintigraphy in case of major renal trauma, serial blood pressure measurements and renal function tests.	C
Manage complications initially by medical management and minimally invasive techniques.	C
Decide on long-term follow-up on a case-by-case basis.	C

4.1.5 Renal injury in the multitrauma patient

Approximately 8-10% of blunt and penetrating abdominal injuries involve the kidneys. The incidence of associated injury in penetrating renal trauma ranges from 77% to 100%. Gunshot wounds are associated with adjacent organ injury more often than stab wounds. Most patients with penetrating renal trauma have associated adjacent organ injuries that may complicate treatment. In the absence of an expanding haematoma with haemodynamic instability, associated multiorgan injuries do not increase the risk of nephrectomy [31]. Blunt and penetrating injuries contribute equally to combined renal and pancreatic injury. Renal preservation is achieved in most patients, and the complication rate is 15% [132]. A similar rate of complications (16%) is reported in patients with simultaneous colon and renal injury [133]. Renal injuries seem to be rare in patients with blunt chest trauma [99].

4.1.5.1   Recommendations for multitrauma patient management

Recommendations	GR
Evaluate multitrauma patients with associated renal injuries on the basis of the most significant injury.	C
In cases surgical intervention is chosen, manage all associated abdominal injuries during the same session.	C
Decide on conservative management following a multidisciplinary discussion.	C

*4.1.6   **Iatrogenic renal injuries***
4.1.6.1   Introduction
Iatrogenic renal trauma is rare, but can lead to significant morbidity.

4.1.6.2   Incidence and aetiology
The commonest causes of iatrogenic renal injuries are listed in Table 4.1.2 [134].

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 [135]. Renal artery and intraparenchymal pseudo-aneurysms (0.9%) may be caused by percutaneous biopsy, nephrostomy, and partial nephrectomy (0.43%) [136]. In 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 arteriocaliceal 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% [137]. Predisposing factors include hypertension, renal medullary disease, central biopsies, and numerous needle passes [138]. Arteriovenous fistulae and pseudo-aneurysms can occur in 1-18% of allograft biopsies [135].

Extrarenal 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 postoperative period [139].

Iatrogenic renal trauma associated with endopyelotomy is classified as major (vascular injury), and minor (urinoma) [140]. 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 [141]. Renal foreign bodies, with retained sponges or wires during open or endourological procedures, are uncommon.

4.1.6.3   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 postoperative bleeding may be caused by interlobar and lower-pole arterial lesions, AVF and post-traumatic aneurysms [142]. 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 [143]. 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 [144]. 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. MRI clearly shows the characteristic features [145]. 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 [146].

4.1.6.4   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. CT can also successfully guide repositioning of the catheter into the collecting system [147]. 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 [148].

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 [149]. 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. Superselective embolisation is required in less than 1% of cases and has proved effective in more than 90% [150]. Short-term deleterious effects are more pronounced in patients with a solitary kidney, but long-term follow-up shows functional and morphological improvements [151]. 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 [152]. 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 [153]. If conservative measures fail in cases of pseudo-aneurysm and clinical symptoms or a relevant decrease in haemoglobin occurs, transarterial embolisation should be considered [154]. As the success rate is similar for initial and repeat interventions, a repeat intervention is justified when the clinical course allows this [89].

Traditionally, patients with postoperative 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 [155].

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 [156]. Superselective embolisation with a coaxial catheter and metallic coils helps to limit the loss of

normal functioning graft tissue [157]. 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 [158]. 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 [159]. 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 [160]. The true nature of lesions caused by foreign bodies is revealed after exploration.

4.1.6.5   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	GR
Treat patients with minor injuries conservatively.	B
Treat severe or persistent injuries with embolisation.	B
In stable patients, consider a second embolisation in case of failure.	C

4.1.7 Algorithms

Figures 4.1.1 and 4.1.2 show the suggested treatment of blunt and penetrating renal injuries in adults.

Figure 4.1.1: Evaluation of blunt renal trauma in adults
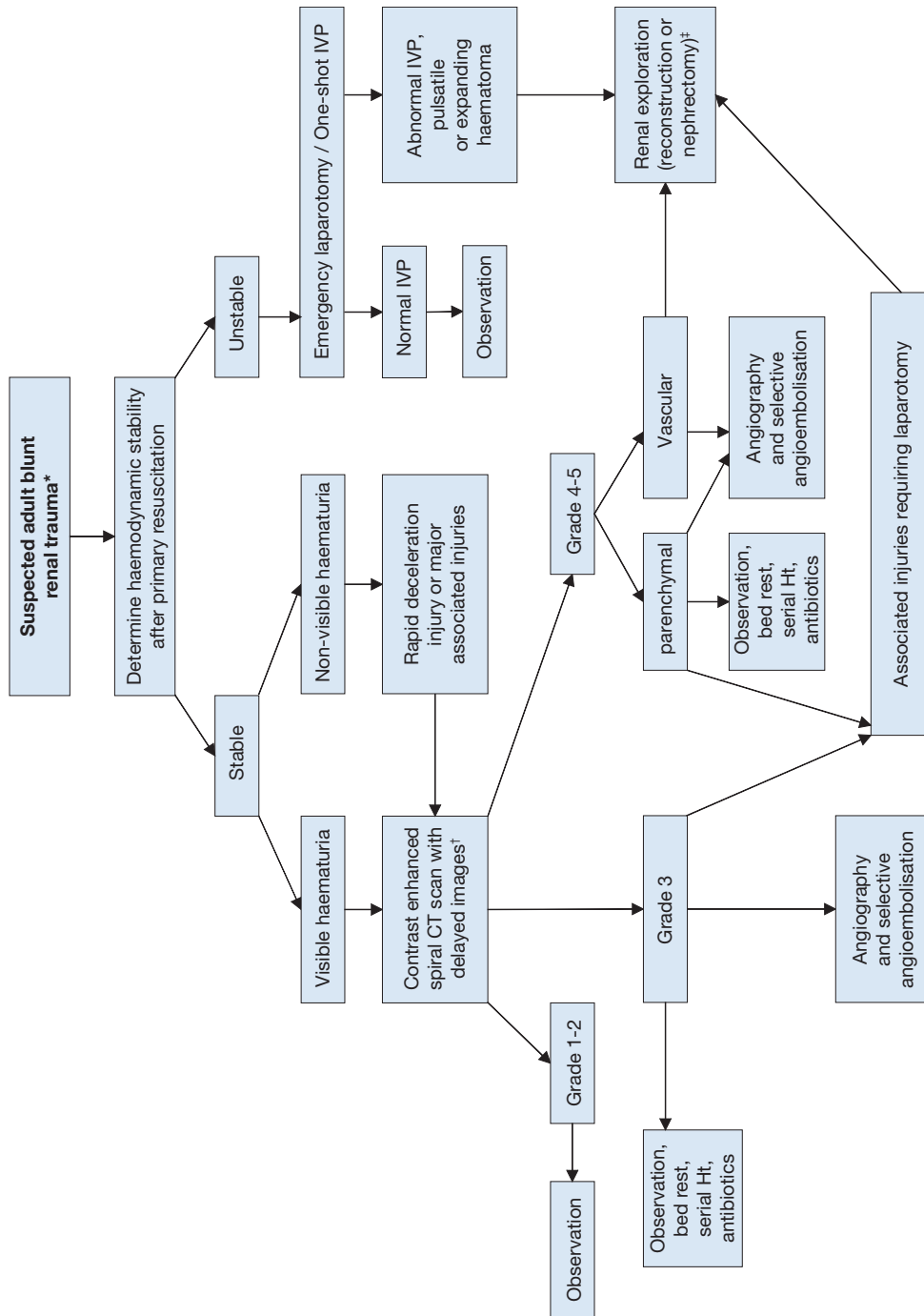
* Suspected renal trauma results from reported mechanism of injury and physical examination.
† Renal imaging: CT scans are the gold standard for evaluating blunt and penetrating renal injuries in stable patients. In settings where CT is not available, the urologist should rely on other imaging modalities (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

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                    ┌─────────────────────────┐
                    │ Evaluation of penetrating│
                    │     renal trauma*        │
                    └───────────┬─────────────┘
                                │
                    ┌───────────▼─────────────┐
                    │ Determine haemodynamic   │
                    │       stability          │
                    └──────┬───────────┬───────┘
                           │           │
                    ┌──────▼───┐  ┌────▼─────┐
                    │  Stable  │  │ Unstable │
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                          │            │
              ┌───────────▼──┐   ┌─────▼──────┐
              │Contrast      │   │ Emergency  │
              │enhanced      │   │ laparotomy │
              │spiral CT scan │   └─────┬──────┘
              │with delayed   │         │
              │images†        │   ┌─────▼────────────┐
              └──┬────┬────┬──┘   │ Renal exploration │
                 │    │    │      │ (reconstruction or│
          ┌──────▼┐ ┌─▼──┐ ┌▼────┐│  nephrectomy)‡    │
          │Grade  │ │Grade│ │Grade││                  │
          │1-2    │ │3    │ │4-5  │└──────────────────┘
          └──┬────┘ └──┬──┘ └─────┘
```

A decision flowchart. Starting from "Evaluation of penetrating renal trauma*", leading to "Determine haemodynamic stability", branching into "Stable" and "Unstable". Stable leads to "Contrast enhanced spiral CT scan with delayed images†", which branches to "Grade 1-2", "Grade 3", and "Grade 4-5". Grade 1-2 and Grade 3 lead to "Observation, bed rest, serial Ht, antibiotics" and "Associated injuries requiring laparotomy". Grade 4-5 and Associated injuries requiring laparotomy lead to "Renal exploration (reconstruction or nephrectomy)‡". "Observation, bed rest, serial Ht, antibiotics" and "Associated injuries requiring laparotomy" lead to "Angiography and selective angioembolisation". Unstable leads to "Emergency laparotomy" then to "Renal exploration (reconstruction or nephrectomy)‡".

* 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.

4.2 Ureteral Trauma

4.2.1 Incidence

Trauma to the ureters is relatively rare because 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. It is seen in open, laparoscopic or endoscopic surgery and is often missed intraoperatively. 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 [16, 161-163], with even higher rates in modern combat injuries [164]. Penetrating external ureteral trauma, mainly caused by gunshot wounds, dominates most of the modern series, both civilian and military [16, 161, 165]. About one-third of cases of external trauma to the ureters are caused by blunt trauma, mostly road traffic injuries [162, 163].

Ureteral injury should be suspected in all cases of penetrating abdominal injury, especially gunshot wounds, because it occurs in 2-3% of cases [161]. It should also be suspected in blunt trauma with deceleration mechanism, when the renal pelvis can be torn away from the ureter [161]. In external ureteral injuries, their distribution along the ureter varies between series, but it is more common in the upper ureter [16, 162, 163].

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 [165-167]. It usually involves damage to the lower ureter [161, 165, 166, 168]. 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 [169]. The incidence of urological iatrogenic trauma has decreased in the last 20 years [165, 170] 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 [165, 169, 171]. Occult ureteral injury occurs more often than reported and not all injuries are diagnosed intraoperatively. In gynaecological surgery, if routine intraoperative cystoscopy is used, the detection rate of ureteral trauma is five times higher than usually reported [171, 172].

Table 4.2.1: Incidence of ureteral injury in various procedures

Procedure	Percentage %
Gynaecological [168, 172-174]	
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 [167, 172, 175]	0.15 - 10
Ureteroscopy [170]	
Mucosal abrasion	0.3 – 4.1
Ureteral perforation	0.2 – 2.0
Intussusception/avulsion	0 – 0.3
Radical prostatectomy [176]	
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 intraoperatively during laparotomy [177], while it is delayed in most blunt trauma and iatrogenic cases [165, 168, 178].

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 [162, 163]. Haematuria is an unreliable and poor indicator of ureteral injury, as it is present in only 50-75% of patients [161, 165, 179].

Iatrogenic injury may be better noticed during the primary procedure, when intravenous dye (e.g. indigo carmine) is injected to exclude ureteral injury. 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 [161, 164, 178]. Early recognition facilitates immediate repair and provides better outcome [174, 180].

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 gold standard for confirmation [165]. Intravenous pyelography, especially one-shot IVP, is unreliable in diagnosis, as it is negative in up to 60% of patients [161, 165].

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 intraoperative dissection in their proximity [165-167]. The use of prophylactic preoperative ureteral stent insertion assists in visualisation and palpation and is often used in complicated cases (about 4% in a large cohort [181]. It is probably also advantageous in making it easier to detect ureteral injury [166]; however, it does not decrease the rate of injury [165]. Apart from its evident disadvantages (potential complications and cost),

a stent may alter the location of the ureter and diminish its flexibility [166, 175]. Routine prophylactic stenting is generally not cost-effective [166]. Another form of secondary prevention is intraoperative cystoscopy after intravenous dye injection, which can provide confirmation of ureteral patency [168]. Routine cystoscopy has minimal risks and can markedly increase the rate of ureteral injury detection [172].

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 [165]. 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 [182]. Injuries that are diagnosed late are usually treated first by a nephrostomy tube with or without a stent [165]. Retrograde stenting is often unsuccessful in this setting.

The endourological treatment of small ureteral fistulae and strictures is safe and effective in selected cases [183], but an open surgical repair is often necessary. 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 [161]. 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 reimplantation (ureteroneocystostomy) because the primary trauma usually jeopardises the blood supply to the distal ureter. The question of refluxing vs. non-refluxing ureteral reimplantation 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 of ureteral repair, the kidney can be relocated to the pelvis (autotransplantation). The renal vessels are anastomosed to the iliac vessels and a ureteral reimplantation 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 reimplantation and a Boari flap
Lower ureter	Ureteral reimplantation
	Ureteral reimplantation 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 motor vehicle accidents account for most of 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
Preoperative prophylactic stents do not prevent ureteral injury, but may assist in its detection.	2
Endourological treatment of small ureteral fistulae and strictures is safe and effective.	3
Major ureteral injury requires ureteral reconstruction following temporary urinary diversion.	3

Recommendations	GR
Visually identify the ureters and meticulously dissect in their vicinity to prevent ureteral trauma during abdominal and pelvic surgery.	A*
In all abdominal penetrating trauma, and in deceleration-type blunt trauma, beware of concomitant ureteral injury.	A*
Only use preoperative prophylactic stents in selected cases (based on risk factors and surgeon's experience).	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):
- Intraperitoneal;
- Extraperitoneal;
- Combined intra-extraperitoneal.

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 [17, 189-191]. Between 60-90% of patients with bladder injuries caused by blunt trauma have associated pelvic fractures, and 44% of patients with bladder injuries have at least one other intra-abdominal injury [192]. Pelvic fractures are associated with bladder injuries in only 3.6% of cases [17]. The majority of ruptures are extraperitoneal, followed by intraperitoneal ruptures and combined intra- and extra-peritoneal ruptures [190, 192]. A combination of bladder and urethral injury is present in 4.1-15% of cases [17, 190].

Extraperitoneal ruptures are almost always associated with pelvic fractures [191]. 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 fractures of the rami pubis [17, 193]. An isolated acetabular fracture is not likely to be associated with bladder injury [193].

Intraperitoneal ruptures are caused by a sudden rise in intravesical pressure, 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]. A full bladder is a risk factor for intraperitoneal ruptures [190]. Penetrating injuries, mainly gunshot wounds, are rare except in conflict regions and some urban settings [189, 194, 195].

4.3.2.2 *Iatrogenic bladder trauma*

The bladder is the urological organ that most often suffers iatrogenic injury [196]. Table 4.3.2 shows the incidence of iatrogenic bladder trauma during various procedures.

Table 4.3.2: Incidence of iatrogenic bladder trauma during various procedures

Procedure	Percentage (%)
External	
Obstetrics	
Caesarean delivery [197, 198]	0.0016-0.94
Gynaecology	
Laparoscopic sterilisation [190]	0.02
Diagnostic laparoscopy [190]	0.01
Laparoscopic hysterectomy [199]	0.05-0.66
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
Urology	
Retropubic male sling [203]	8.0-50
Laparoscopic sacrocolpopexy [204]	1.9
Burch colposuspension [205, 206]	1.0-1.2
Midurethral sling (transobturator route) [205, 207]	0-2.4
Midurethral sling (retropubic route) [205, 207]	3.2-8.5
Pubovaginal sling [205]	2.8
Transvaginal mesh surgery [208, 209]	1.5-3.5
Anterior colporrhaphy [209]	0.5
TURB [210, 211]	3.5-58
TURP [190]	0.01

TURB = transurethral resection of the bladder; TURP = transurethral resection of the prostate.

External iatrogenic bladder trauma occurs most often during obstetric and gynaecological procedures, followed by general surgical and urological interventions [196]. Main risk factors are previous surgery, inflammation and malignancy [196].

Internal iatrogenic bladder trauma mainly occurs during transurethral resection of bladder tumour (TURB). Reported risk factors are larger tumours, older age, pre-treated bladders (previous TURB, intravesical instillations) and location at the bladder dome [212, 213]. Monopolar TURB at the lateral wall with inadequate muscle relaxation and subsequent risk of stimulation of the obturator nerve also increases the risk of perforation. Perforations requiring intervention are rare (0.16-0.57%) [212]. Extraperitoneal perforations are more frequent than intraperitoneal perforations [213, 214].

Intravesical foreign bodies include:
- Retained parts of endourologic equipment such as resectoscopes, ureteric stents or bladder catheters;
- Forgotten pieces of surgical gauze, sutures or staples used in pelvic procedures [215, 216];
- An unrecognised perforation or erosion of mesh used for correction of urinary incontinence or pelvic organ prolapse [215].

4.3.3 Diagnostic evaluation
4.3.3.1 General evaluation
The cardinal 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 [217], and this combination is an absolute indication for further imaging [190, 217] (LE: 3). However, approximately 5-15% of patients with bladder rupture only have non-visible haematuria [193]. Existing data do not support lower urinary tract imaging in all patients with pelvic fracture or non-visible haematuria alone. In visible haematuria without pelvic fracture, non-visible haematuria with pelvic fracture and isolated nonvisible haematuria, the decision for further imaging should be based on the presence of other clinical signs and symptoms and the site of maximal trauma [190]. Clinical signs and symptoms 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 = cardinal sign
Inability to void [190, 218]	
Abdominal tenderness [191]	
Suprapubic bruising [190, 218]	
Abdominal distension [190, 218]	In the case of urinary ascites
Swelling of scrotum, perineum, abdominal wall and/or thighs [190]	
Uraemia and elevated creatinine level [190]	Intraperitoneal rupture => reabsorption of urea nitrogen and creatinine
Entrance/exit wounds at lower abdomen, perineum or buttocks [194, 218]	In penetrating injuries

Signs of external iatrogenic bladder trauma 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 [190, 197]. Direct inspection is the most reliable method of assessing bladder integrity [196]. Intravesical instillation of methylene blue may be helpful [197]. If bladder perforation is close to the trigone, the ureteric orifices should be inspected [190, 196].

Internal iatrogenic bladder trauma is suggested by cystoscopic identification of fatty tissue, a dark space between detrusor muscle fibres, or the visualisation of bowel [210]. Signs of major perforation are the inability to distend the bladder, a low return of irrigation fluid, and abdominal distension [219].

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 [190, 196]. An iatrogenic bladder trauma during hysterectomy can be complicated by a vesicovaginal fistula [220].

Symptoms of an intravesical foreign body include dysuria, recurrent urinary tract infection, frequency, urgency, haematuria, and perineal/pelvic pain [215]. Bladder calculi usually develop once the foreign body has been present > three months [215, 221].

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

iatrogenic bladder trauma in the post-operative setting [220, 222]. Both plain and CT cystography have a comparable sensitivity (90-95%) and specificity (100%) [191, 223]. Computed tomography cystography may identify other injuries or causes of abdominal pain [190].

Cystography must be performed using retrograde filling of the bladder with a minimum volume of 350 mL of dilute contrast material [220, 222].

With intraperitoneal extravasation, free contrast medium is visualised in the abdomen, highlighting bowel loops and/or outlining abdominal viscera such as the liver [190, 224]. Extraperitoneal bladder injury is associated with flame-shaped areas of contrast extravasation in the perivesical soft tissues [190]. Contrast medium in the vagina is a sign of vesicovaginal fistula [220].

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 [206, 225]. Routine cystoscopy after sling insertion through the obturator route is controversial because bladder injuries are rare but not impossible [206, 225]. Cystoscopy after transvaginal mesh procedures is preferable, but not mandatory [226].

Cystoscopy is preferred to diagnose a foreign body [216, 221].

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 [190].

4.3.4 Disease management
4.3.4.1 Conservative management
Conservative treatment comprises clinical observation, continuous bladder drainage and antibiotic prophylaxis [190, 213]. This is the standard treatment for an uncomplicated extraperitoneal injury due to blunt trauma, after TURB or after other operations in which the injury was not recognised during surgery [190, 213, 218].

It is an option for an uncomplicated intraperitoneal injury after TURB or not recognised during surgery, but only in the absence of peritonitis and ileus [211, 224]. In addition to conservative treatment, placement of an intraperitoneal drain has been advocated, especially when the lesion is larger [219, 227].

4.3.4.2 Surgical management
The preferred method is two-layer vesicorraphy (mucosa-detrusor) with absorbable sutures [190, 196].

4.3.4.2.1 Blunt non-iatrogenic trauma
Although most extraperitoneal ruptures can be treated conservatively, bladder neck involvement, bone fragments in the bladder wall, concomitant rectal injury or entrapment of the bladder wall will necessitate surgical intervention [190, 218] (LE: 3). 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, 218] because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death [192] (LE: 3). Abdominal organs should be inspected for possible associated injuries and urinomas must be drained if detected. In the absence of other intraabdominal injuries, laparoscopic suturing of the intraperitoneal rupture is possible [191].

4.3.4.2.2 Penetrating non-iatrogenic trauma
The standard treatment is emergency exploration, debridement of devitalised bladder muscle and primary bladder repair (LE: 3) [194, 195]. A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters [190, 194]. In gunshot wounds, there is a strong association with intestinal and rectal injuries, requiring faecal diversion [194]. 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].

4.3.4.2.3   Non-iatrogenic bladder trauma with avulsion of the lower abdominal wall or perineum and/or bladder tissue loss

In these cases, direct closure of the traumatised bladder will lead to excessive tension, resulting in ischaemia and eventually breakdown of the repair. A bladder wall substitute is needed to repair the bladder defects and to restore the lower abdominal wall or perineum. A pedicled vastus lateralis myocutaneous flap has been proposed for this [211, 228].

4.3.4.2.4   Iatrogenic bladder trauma

Perforations recognised intra-operatively are primarily closed.

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 [190, 224]. If surgical exploration is performed after TURB, the bowel must be inspected to rule out concomitant injury [212]. For extraperitoneal injuries, exploration is only needed for large perforations complicated by symptomatic extravesical collections. It requires drainage of the collection, with or without closure of the perforation [229].

If bladder perforation is encountered during midurethral sling or transvaginal mesh procedures, sling re-insertion and urethral catheterisation (one-two days) should be performed [230].

4.3.4.2.5   Intravesical foreign body

For perforated or eroded meshes, the intravesical portion must be removed by open cystotomy or endoscopically [221, 231]. The choice depends on the surgeon's level of experience and the location of the mesh [221, 231]. For other types of foreign bodies, cystoscopic removal is performed and if this fails cystotomy is needed [216].

4.3.5   *Follow-up*

Continuous bladder drainage is required to prevent elevated intravesical pressure and to allow the bladder to heal [196, 232]. Conservatively treated bladder injuries (traumatic or external iatrogenic bladder trauma) are followed by planned cystography scheduled to evaluate bladder healing, with catheter removal in case of absence of contrast extravasation [233]. The first cystography is planned 7-14 days after injury, depending on the extent of the laceration, and should be repeated thereafter in the case of an ongoing leakage [233].

After operative repair of a simple injury in a healthy patient, the catheter can be removed after 7-10 days without need for a control cystography [215, 232] (LE: 2a). 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 [215, 232].

For conservatively treated internal iatrogenic bladder trauma, a catheter duration of 5 and 7 days for extraperitoneal and intraperitoneal perforations, respectively, has been proposed [198, 213, 214] (LE: 3).

4.3.6   *Summary of evidence and recommendations for the management of bladder injury*

Summary of evidence	LE
Extraperitoneal bladder perforations are more common than intraperitoneal perforations.	3
The risk of bladder perforation during midurethral 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	GR
Perform cystography to diagnose non-iatrogenic bladder injuries, and suspected, iatrogenic, post-operative, bladder injuries.	B
Use cystography (conventional or CT imaging) in the presence of visible haematuria and pelvic fracture.	B
Actively fill the bladder with at least 350 mL of dilute contrast during cystography.	B
Perform cystoscopy after suburethral sling operations via the retropubic route. It is optional after any other type of sling procedure or transvaginal mesh procedure.	B
In the absence of bladder neck involvement and/or associated injuries that require surgical intervention, manage extraperitoneal bladder ruptures caused by blunt trauma conservatively.	B

Manage intraperitoneal bladder ruptures by blunt trauma and any type of bladder injury by penetrating trauma, by emergency surgical exploration and repair.	B
Initially manage small, uncomplicated, iatrogenic intraperitoneal bladder perforations conservatively.	C

CT = computed tomography; IVP = intravenous pyelogram.

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 [234, 235]. New treatment methods and applied energy sources can also injure the urethra [236].

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 [236, 237], while the bladder neck is rarely affected in such cases [238].

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 [239] (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 [235, 240].

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 unipolar current and the diameter of the instruments used [241].

Predisposing factors most strongly associated with stricture formation in patients undergoing TURP are increased prostate volume, prostate cancer and the surgeon's experience [242]. 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 reapplied when the resection time is prolonged [243]. Internal urethrotomy must be performed before TURP if there are pre-existing meatal or urethral strictures [243].

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 [244].

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 [245, 246]. The Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) database shows an incidence of urethral stricture after various forms of prostate cancer therapy of 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 [245].

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 [247].

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 [248].

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 [249, 250]. Brachytherapy is a recognised cause of strictures in patients with localised prostate cancer, as the CaPSURE study has shown [251]. Previous TURP increases the risk of stricture formation [252, 253].

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 preoperatively to prevent these complications [254]. Radical

cystectomy and subsequent urinary diversion may also cause urethral trauma [255]. 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	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
The greatest risk for urethral stricture is found in the combination of radical prostatectomy and EBRT	
Cryotherapy	
HIFU	
Treatment for bladder disease	
TURB	
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;
EBRT = external-beam radiation therapy; HIFU = high-intensity focused ultrasound.

4.4.1.2   Non-iatrogenic urethral injuries
4.4.1.2.1   Anterior urethral injuries (in males)
Different causes of anterior injuries [256] are depicted in Table 4.4.2. Anterior urethral injuries are mainly caused by blunt trauma [256-258], with the bulbar urethra being the most common site injured [258, 259]. 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 [260].

Penetrating injuries of the penile or bulbar urethra are rare and usually caused by gunshot wounds [260-265]. Depending on the affected segment, penetrating injuries are usually associated with penile, testicular and/or pelvic injuries [262, 265].

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 [261]. Penile fractures account for 10-20% of anterior injuries [261]. In up to one-third of cases, the tear extends into the corpus spongiosum and urethra [266]. 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 [267, 268].

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 (about 72%) [267, 268], which themselves are usually caused by motor vehicle accidents [17, 234, 269]. Iatrogenic posterior injuries, due to irradiation or surgery to the prostate, are an increasing problem [267, 268], but appear to be less common than previously believed (3-25%) [256].

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 [234]. There is no urethral wall in the scarred space and any lumen represents merely a fistulous tract between the urethral stumps [234]. Injury to the posterior urethra exclusively occurs in pelvic fractures with disruption of the pelvic ring [17]. 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 [270]. Displaced fractures of the inferomedial pubic bone and pubic symphysis diastasis, together with their degree of displacement, are independent predictors of urethral injury [269]. Injuries of the bladder neck and prostate are rare [271] 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 [271].

Penetrating injuries of the pelvis, perineum or buttocks (mainly gunshot wounds) can also cause damage to the posterior urethra, but are extremely rare [272]. There is a high probability of associated injuries (80-90%), mainly intraabdominal [194, 272].

Although urethral injuries themselves are not directly life-threatening [17, 256], the association with pelvic fractures and concomitant injuries of the thorax, abdomen and spine, may be life-threatening [17, 269].

Delayed morbidity of posterior urethral injuries includes strictures, incontinence and erectile dysfunction (ED), which may all have a detrimental effect on the quality of life [273]. Erectile dysfunction occurs in approximately 45% of patients after traumatic posterior urethral rupture [273, 274]. Strong predictors for ED are diastasis of the pubic symphysis [273-275], lateral displacement of the prostate [273, 276], a long urethral gap (> 2 cm) [273], a bilateral pubic rami fracture and a Malgaigne's fracture [273]. 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 [273].

4.4.1.3   *Urethral injuries in females*
Urethral injuries are very rare in females [257, 260]. Pelvic fractures are the main aetiology [257]. The injury is usually a partial longitudinal tear of the anterior wall associated with vaginal laceration [257, 261]. Urethral injuries in females which extend into the bladder neck may disrupt the normal continence mechanism [277].

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 [234]. 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 [234]. In addition, haematuria and pain on urination may be present. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on

the location and extent of the trauma [256, 261]. The presentation of these clinical symptoms may be delayed (> 1 hour) [234].

Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases) [278, 279] and may reveal a 'high-riding' prostate, which is an unreliable finding [234, 278]. Failure to detect a rectal injury can cause significant morbidity and even mortality [278]. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration [278]. Another sign of urethral injury is difficulty or an inability to pass a urethral catheter [278].

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 [257, 260, 261]. Vaginal examination is indicated to assess vaginal lacerations [278].

Symptoms of urethral lesions caused by improper catheterisation or instrumentation are penile and/or perineal pain (100%) and urethral bleeding (86%) [238]. Failure to accurately diagnose and treat urethral injuries may lead to significant long-term sequelae, mostly presenting as strictures [280, 281].

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 [256]. 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 [256, 261]. In an unstable patient, retrograde urethrography should be postponed until the patient has been stabilised [194, 257].

A urethrogram allows for identification of the site of injury and assessment of the extent of any injury [278]. Any extravasation outside the urethra is pathognomonic for urethral injury. However, the distinction between a complete and partial rupture is not always clear [234]. 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 [234].

The following classification of urethral injuries is based on retrograde urethrography (Table 4.4.3) [256]:

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 [256].

4.4.2.2.2 Ultrasound, computed tomography and magnetic resonance (MRI) imaging
In the acute phase, US scanning is used for guiding the placement of a suprapubic catheter [256]. Computed tomography and rarely MRI are useful to evaluate concomitant injuries [256, 261].

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 [256]. In addition, it may allow a guidewire to be passed into the bladder for early catheterisation [257, 282]. Flexible cystoscopy is also recommended above retrograde urethrography in suspected penile fracture-associated urethral injury [277, 283, 284]. In females, where the short urethra precludes adequate, radiological visualisation, urethroscopy and vaginoscopy are the diagnostic modalities of choice [256, 257].

4.4.2.3 Summary
Prior to deferred management, the combination of retrograde urethrography and antegrade cystourethrography is standard [256]. The location and extent of the obliteration is diagnosed [256]. An MRI of the pelvis provides valuable additional information, which can help to determine the most appropriate surgical strategy [256,

276]. If the competence of the bladder neck is not clear upon antegrade cystourethrography, a suprapubic cystoscopy is advised [256].

4.4.3   *Disease Management*
4.4.3.1   *Anterior urethral injuries*
Anterior urethral injuries are usually not associated with other life-threatening injuries [257, 261]. 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 [256]. The therapeutic options are suprapubic diversion or (a trial of) early endoscopic realignment with transurethral catheterisation [257]. Urinary diversion is maintained for two and three weeks for partial and complete ruptures, respectively [259].

Satisfactory urethral luminal recanalisation may occur in up to 68% after partial ruptures, but is rare after complete ruptures [259, 285].

4.4.3.1.2   Penile fracture-related anterior urethral injuries
In order to preserve erectile function, penile fractures require early exploration [260, 277, 286, 287]. 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 [286]. In these circumstances, there is no substantial urethral tissue loss [288]. A small laceration can be repaired by simple closure, while a complete rupture requires an anastomotic repair [286, 287].

4.4.3.1.3   Penetrating anterior urethral injuries
Immediate exploration is advised, except when this is precluded by other life-threatening injuries [256]. Devitalised tissues should be debrided, although urethral and spongiosal debridement should be kept to a minimum due to the excellent vascularisation [265, 277]. For small lacerations and stab wounds, simple urethral closure might be sufficient [256]. 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 [257, 263, 265]. In the case of longer defects or apparent infection (particularly bite wounds), a staged repair with urethral marsupialisation and a suprapubic catheter is needed [263, 265]. Peri- and post-operative antibiotic treatment is also necessary [264].

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 [256, 257]:
*   Immediate: < 48 hours after injury (4.4.3.2.1.1);
*   Delayed primary: 2 days to 2 weeks after injury (4.4.3.2.1.2);
*   Deferred: > 3 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 [234, 257]:
*   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 [256, 277]. 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 [234, 257, 261, 267, 268, 288]. If there is any difficulty, a suprapubic catheter should be placed under US guidance and direct vision [234].

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 [277].

Urethrography should be performed at two-weekly intervals until healing has occurs [279, 289]. Injuries may heal without significant scarring or obstruction if managed by diversion alone [277]. 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 [285, 290].

4.4.3.2.1.1.2 Complete posterior urethral rupture
Acute definitive treatment options include:
- Immediate realignment: 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 realignment
The aim of realignment is to correct severe distraction injuries rather than to prevent a stricture [277].
The reported benefits of realignment are:
- A lower stricture rate than with suprapubic catheter placement alone (where stricture formation is almost certain) [285, 290, 291];
- 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 [285, 290, 292]. For longer strictures, or in the case of failure of an internal urethrotomy, urethroplasty is required [290];
- If urethroplasty is required later, it is technically easier when the prostate and urethra are well aligned [293].

Endoscopic realignment is the preferred technique 87-95 [257, 277]. 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) [285, 290, 291]. The duration of catheter stay varies between 4 and 8 weeks among series [278, 285, 290, 291].

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 the 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 realignment can also be performed when the patient is on the operating table for other surgery. Early endoscopic realignment (immediate or delayed primary, see below) is also possible in a stable patient without significant concomitant injuries [290, 291].

With modern endoscopic realignment procedures, acceptable complication rates have been reported for stricture formation (14-79%), incontinence (< 5%) and impotence (10-55%) [290, 291].

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 [278, 285, 290, 291].

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, because of extensive swelling and ecchymosis. This might lead to extensive unjustified urethral debridement [257]. Another problem is the risk of uncontrolled bleeding following entry into the pelvic haematoma, which may result in uncontrolled re-bleeding [257]. Due to disturbingly high rates of impotence (56%), incontinence (21%) and strictures (69%) [289], immediate urethroplasty cannot be recommended and should only be done in experienced centres [294, 295].

4.4.3.2.1.1.3 Delayed primary treatment
Delayed treatment options include delayed primary realignment (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 realignment
In the absence of indications for immediate exploration, posterior urethral disruption can be managed in a delayed primary fashion. Delayed primary realignment requires the placement of a suprapubic tube at the time of initial injury, with endoscopic realignment performed within 14 days (i.e. before fibrosis begins). At that time, patients are stable and most of the pelvic bleeding has resolved [289, 291]. The aim and proposed benefits of delayed primary realignment are the same as mentioned for immediate realignment. Endoscopic realignment is also the preferred modality.

4.4.3.2.1.1.3.2 Delayed primary urethroplasty
Delayed primary urethroplasty is performed no later than 14 days after the initial injury i.e. before the start of the fibrotic process [296, 297]. If successful, it avoids a long period of suprapubic diversion [296]. It is restricted to stable patients with a short distraction defect, who are able to lie down in the lithotomy position [296]. Considering the limited accumulated experience with this approach, it cannot be generally recommended [296, 298, 299].

Supporters of early vs. delayed intervention state that it does not affect the outcome of an eventual subsequent urethroplasty [294, 300]. However, some authors have reported worse outcomes of subsequent urethroplasty after failed initial urethral manipulation (realignment or urethroplasty) [295, 296, 301]. Due to this concern and the excellent results obtained with deferred urethroplasty, early realignment or urethroplasty should only be selectively performed in highly experienced centres [294, 295].

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 [234, 289]. 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 [277]. After 3 months of suprapubic diversion, the pelvic haematoma is nearly always already resolved, the prostate has descended into a more normal position and the scar tissue has stabilised [296] and the patient is clinically stable and able to lie down in the lithotomy position [256, 257].

Most posterior urethral distraction defects are short and can be treated using a perineal anastomotic repair [256, 296]. 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) [277, 296].

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 [302] with reported success rates of 80-98% [303-305].

Most urethral stenoses are short and can be treated by mobilisation of the bulbar urethra, with or without separation of the corpora cavernosa [296]. 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 rerouting or a combined abdominoperineal approach are needed more often [292, 304].

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) [306, 307].

Table 4.4.4: Circumstances that might preclude successful perineal anastomotic repair, either as an initial or as a salvage therapy [306, 307]

Circumstance	Alternative procedure
Distraction defects longer than 7-8 cm	A tubed interposition flap of penile or perineal skin can be used for reconstruction [308]. This is seldom required and most patients that require flap urethroplasties have previous failed repairs of posterior urethral rupture [277].
Fistulae	These might require a combined abdominoperineal approach to secure adequate closure [304].
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 [256, 277, 304].

Outcome after deferred urethroplasty is excellent with a stricture rate of around 10% [302, 309]. Deferred urethroplasty is unlikely to result in additional ED [296, 309]. Decompression of the erectile nerves after excision of the scar tissue might explain the amelioration of erectile function after urethroplasty [310]. Incontinence is rare with deferred urethroplasty (< 4%) [296] and is usually due to incompetence of the bladder neck [277, 304]. 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 [311, 312] and the procedure is therefore not recommended. For short, non-obliterative strictures following realignment or urethroplasty, direct vision urethrotomy can be performed [305] 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, 272]. If possible, immediate exploration by the retropubic route and primary repair or realignment can be performed [194, 272, 277]. In the case of rectal injury, a diverting colostomy is necessary [194, 272]. Life-threatening associated injuries often preclude direct urethral repair. In those cases, suprapubic diversion with delayed abdominoperineal urethroplasty is advised [194, 265, 272].

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 [257, 260, 278, 279]. Distal urethral injuries can be managed vaginally by primary suturing and closure of the vaginal laceration [257, 279]. In all of these operations, it is advisable to use a flap (e.g. Martius) to prevent urethrovaginal fistulas [313]. Nonetheless, distal urethral injuries can be left unrepaired and hypospadiac since they do not disrupt the sphincteric mechanism [257, 260, 278, 279].

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 [314], although its value in minor urethral injuries is unproven. In difficult cases, catheter insertion may be assisted by cystoscopy and guidewire placement [315], and 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 [316].
        Urethral lesions following radiotherapy are often more difficult to treat and may require complex reconstructive surgery [249, 250]. 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
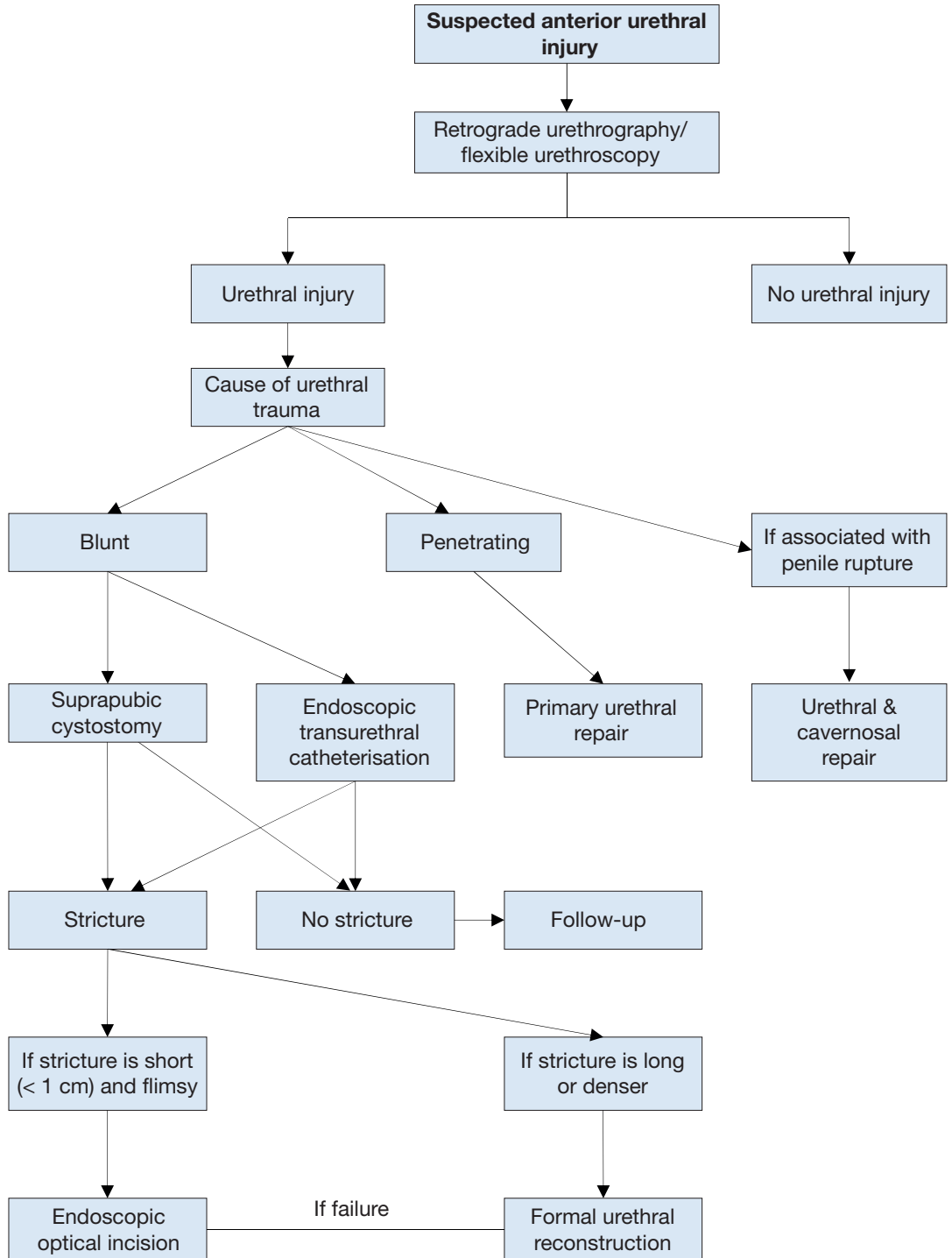
Figure 4.4.2: Management of posterior urethral injuries in men

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                          ┌─────────────────────────┐
                          │ Suspected urethral injury│
                          └────────────┬────────────┘
                                       ↓
                          ┌─────────────────────────┐
                          │  Retrograde urethrogram  │
                          └────────────┬────────────┘
                                       ↓
                          ┌─────────────────────────────┐
                          │ Prostatomembranous disruption│
                          └──────┬───────────────┬──────┘
                    ┌────────────┘               └────────────┐
            ┌───────────────┐                          ┌───────────────┐
            │ Complete rupture│                          │ Partial rupture│
            └──┬──────────┬──┘                          └──┬──────────┬──┘
        ┌──────┘          └──────┐               ┌────────┘          └────────┐
 ┌────────────┐          ┌────────────┐    ┌────────────┐              ┌────────────┐
 │ Penetrating│          │    Blunt   │    │    Blunt   │              │ Penetrating│
 └──────┬─────┘          └──────┬─────┘    └──────┬─────┘              └──────┬─────┘
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- **Penetrating** → Primary open repair. If patient unstable or significant associated non-urological injuries, suprapubic cystostomy

- **Blunt** (Complete rupture) → Assess for acute surgical indications: bladder neck injury, rectal tear, pie-in-the-sky bladder
  - **No** → Suprapubic cystostomy → Option: endoscopic realignment if patient is stable (< day 14) → Delayed urethroplasty
  - **Yes** → Suprapubic tube + endoscopic re-alignment. Open if rectal or bladder injury. → Stricture → Delayed urethroplasty

- **Blunt** (Partial rupture) → Suprapubic cystostomy
  - **Stricture** → Urethrotomy → Stricture → Delayed urethroplasty
  - **No stricture**

- **Penetrating** (Partial rupture) → Primary open repair. If patient unstable or significant associated non-urological injuries, suprapubic cystostomy

Figure 4.4.3: Treatment of iatrogenic urethral injury caused by improper insertion of a catheter
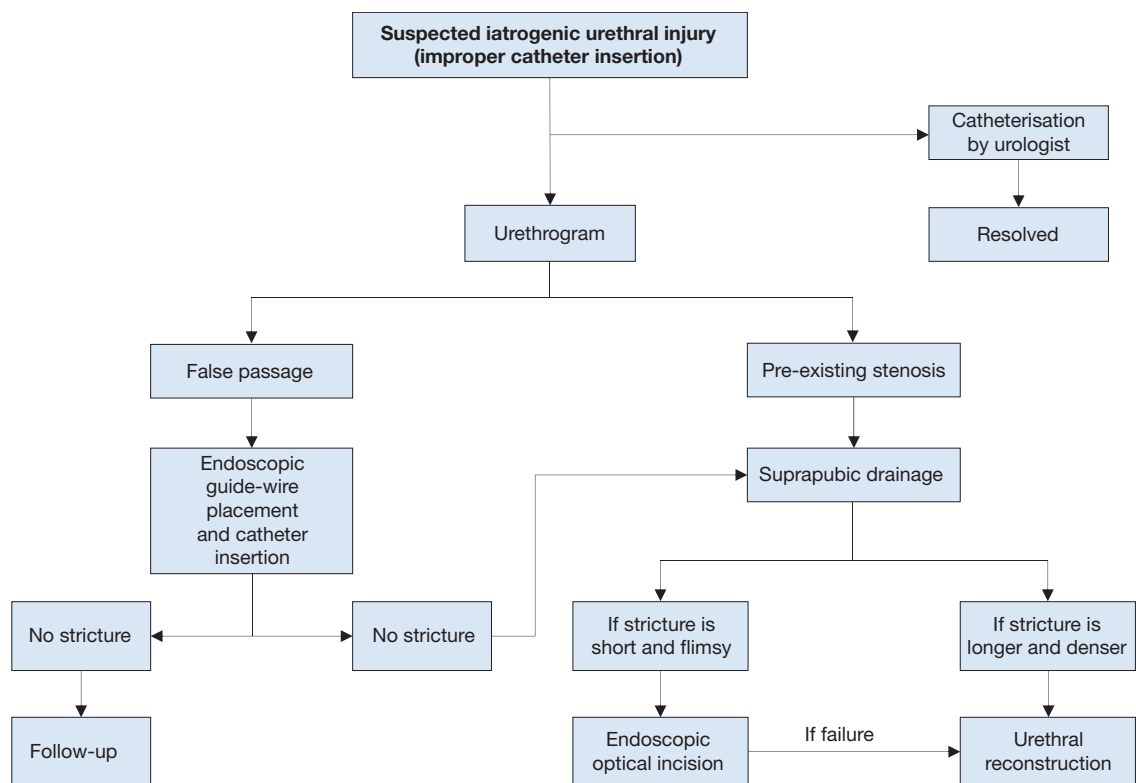
Figure 4.4.4: Treatment for stricture after radical prostatectomy
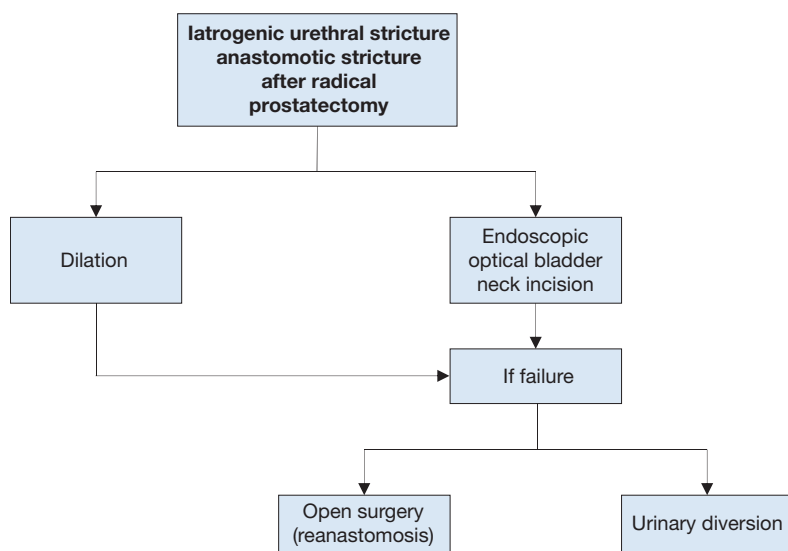
4.4.4   ***Summary of evidence and recommendations for the management of urethral trauma***

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	GR
Use retrograde urethrography to evaluate urethral injuries.	B
Manage posterior urethral defects with delayed formal urethroplasty.	B
Treat partial posterior urethral ruptures by urethral or suprapubic catheterisation.	C
Treat blunt anterior urethral injuries by suprapubic diversion.	C

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.	2b
New technologies represent an additional source of urethral injury.	3

Recommendations	GR
Provide training to reduce the risk of traumatic catheterisation.	A
Only carry out urethral instrumentation when there are valid clinical indications.	A
Ensure that when catheterisation is necessary, its duration is kept to a minimum.	B

4.5   Genital Trauma
4.5.1   Introduction and background
Genito-urinary trauma is seen in both sexes and in all age groups. Of all urological injuries, 33-66% involve the external genitalia [19]. 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 and only approximately 1% present as bilateral scrotal or testicular injuries [317].

Any kind of contact sport, without the use of necessary protective aids, may be associated with genital trauma. Off-road bicycling and motorbike riding (especially on motorbikes with a dominant petrol tank), rugby, football and hockey are all activities which are associated with blunt testicular trauma [318-321].

Penetrating injuries account for 20% of genito-urinary trauma, with 40-60% of all penetrating genito-urinary lesions involving the external genitalia [262, 322]. Thirty-five per cent of all genito-urinary gunshot wounds involve the genitalia [317]. In a recent series of wartime genito-urinary injuries, 71.5% of 361 operations involved the external genitalia - the majority caused by improvised explosive devices (IEDs) and other explosive ordinance, while smaller numbers of injuries were due to gunshot injuries [323]. 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 [317, 324].

Self-mutilation of the external genitalia has also been reported in psychotic patients and transsexuals [325]. 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 [326]. Both male and female genital piercings increase the risk for unexpected genital trauma [327]. Although there is an increased risk of Hepatitis B and C in genitally injured patients, there is no higher incidence of STDs in patients with genital piercing [327].

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 [328, 329]. In women with genital injuries and blood at the vaginal introitus, further gynaecological investigation is needed to exclude vaginal injuries [329]. 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 [19].

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 multicida*, which accounts for up to 50% of infections [330]. Other commonly involved organisms are *Escherichia coli, Streptococcus viridans, Staphylococcus aureus, Eikenella corrodens, Capnocytophaga canimorsus Veillonella parvula, Bacteroides* and *Fusobacterium spp.* [325, 330, 331].

The first choice of antibiotics is penicillin-amoxiclavulanic acid, followed by doxycycline, cephalosporin or erythromycin for 10-14 days [332-334]. 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 [335, 336].

4.5.2.2.2 Human bites

Human bites are much less common, but infection should be considered, especially in 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 [337].

4.5.2.3 Sexual assault

Genital injury is often seen (42%) after sexual abuse, which must be considered when genital injuries present at any age [338]. 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 [339] 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 [340, 341].

*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. This results from trauma to the erect penis during sexual intercourse, masturbation, rolling over in bed (rarely) and as a result of self-inflicted bending to produce detumescence in some Middle Eastern Cultures - a practice known as 'taqaandan' (which, when translated, means 'to click') [342]. 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 [343], and is 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% [344, 345].

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 [346, 347]. 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.

A thorough history and examination usually confirm the diagnosis, but in some cases imaging may be useful. Cavernosography, US or MRI [348-350] can identify lacerations of the tunica albuginea in unclear cases [351], or provide reassurance that the tunica is intact. If a concomitant urethral injury is suspected, a retrograde urethrogram (RUG) may be performed, even though 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 [352].

When a penile fracture is diagnosed, surgical intervention with closure of the tunica albuginea is recommended. The approach is usually through a circumferential incision proximal to the coronal sulcus which enables degloving the penis entirely. Increasingly, local longitudinal incisions centred on the area of fracture are currently used and further localisation may be gained with a flexible cystoscopy performed prior to incision, if urethral trauma is suspected and eventually proven.

Closure can be obtained by using absorbable sutures, with good long-term outcome, and protection of potency. Post-operative complications were reported in 9%, including superficial wound infection and impotence in 1.3% [343, 353]. The conservative management of penile fracture is not recommended. It increases complications, such as penile abscess, missed urethral disruption, penile curvature, and persistent haematoma requiring delayed surgical intervention [353]. Late complications after conservative management were fibrosis and angulations in 35% and impotence in up to 62% [343, 353].

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 [262]. 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 [325].

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 [325]. 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 [352]. 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.

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 [354]. 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 little or non-functioning penile stump.

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 occurs rarely. It is most common in victims of MVAs [355-358]. Bilateral dislocation of the testes has been reported in up to 25% of cases [356]. 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 haematoceles smaller than three times the size of the contralateral testis [359]. In large haematoceles, non-operative management often fails, and delayed surgery (> three days) is often required. Patients with large haematoceles have a higher rate of orchiectomy than patients who undergo early surgery, even in non-ruptured testes [317, 325, 360-362]. 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 [362]. In addition, non-operative management is also associated with prolonged hospital stays. Therefore, large haematoceles 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 [362]. 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 [363]. 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.

High-resolution, real-time US with a high-resolution probe (minimum 7.5 MHz or higher) should be performed to determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture [364-371]. 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% [347]. Others reported poor specificity (78%) and sensitivity (28%) for the differentiation between testicular rupture and haematocele, while accuracy is as low as 56% [365]. 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 [372]. 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, realignment without vaso-vasostomy may be considered if surgically feasible [373]. Staged secondary microsurgical vaso-vasostomy can be performed after rehabilitation, although only a few cases have been reported [373]. 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 [262].

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 [325]. 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 [323].

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 [329, 339].

4.5.5.1 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 [374]. 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% [328].

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 [375], 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 [376].

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 [329]. Flexible or rigid cystoscopy has been recommended to exclude urethral and bladder injury [328, 329]. 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	GR
In penile fracture, treat with early surgical management, with closure of tunica albuginea, to enable good long-term outcome and preservation of potency.	B
In testicular trauma, perform surgical exploration in all cases of testicular rupture and in those with equivocal imaging.	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 [377]. Lessons from civilian trauma networks, the battlefield, and mass casualty events have led to many advances in general trauma care [378, 379]. 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 [380]. Major trauma patients initially managed in local hospitals are 1.5 to 5 times more likely to die than patients transported directly to specialist trauma centres. The reorganisation of care to these centres has been shown to reduce mortality by 25% and length of stay by four days [378]. 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 [381].

5.1.1.1 Recommendations for polytrauma management

Recommendation	GR
Manage polytrauma patients in designated major trauma centres.	A*
Ensure involvement of urologists in cases of associated urological injury.	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 [382-384].
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 [385].

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 [386]. 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 [383, 387].

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 minimizing 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 the severely injured polytrauma patient.	4

Recommendation	GR
Follow damage control principles in the management of severe polytrauma patients.	A*

*Upgraded following panel consensus.

5.4 Urological injury management in polytrauma

5.4.1 ***Renal injury***

The incidence of multiorgan injury is high in penetrating trauma [31]. Most of these injuries can be managed without surgical exploration [28]. Renal exploration is required to control life-threatening bleeding [388]. The preservation of viable renal parenchyma is a secondary goal, with time-consuming renal reconstruction delayed until the patient is optimised [111].

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 [78]. In unstable patients, packing the renal fossa and transferring the patient to the surgical ICU is the option of choice for damage control. A planned second-look laparotomy is then performed [182]. 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 [389].

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 [182].
- Haemostatic agents, i.e. combined acellular matrix and fibrin sealants [113].
- Absorbable mesh kidney bags to maintain contact between renal parenchymal fragments [106].
- An intra-operative drain is left *in situ* to collect any urine that leaks following organ salvage.

5.4.1.2 *Recommendations for the management of renal injury*

Recommendations	GR
Manage life-threatening bleeding from renal injury by urgent nephrectomy.	B
Manage profuse non-arterial bleeding by renal packing as a damage control measure.	B
Use angioembolisation as an effective haemostatic measure.	B

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 [165]. A high index of suspicion is required as these injuries are quite commonly missed [390]. 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 [111, 182].
        Tying off the injured ureteral segment and inserting a percutaneous nephrostomy post-operatively is a viable alternative [391]. 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	GR
Rule out ureteral injury in penetrating abdominal trauma.	A
Treat ureteral injury with 'tube' urinary diversion if repair is not performed.	C

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 [190]. 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 [182];
• Packing and/or arteriography and selective embolisation in unstable patients with severe bladder haemorrhage [182];
• The placement of a pelvic suction drain for urinary evacuation [182].

5.4.3.1   Recommendations for the management of bladder trauma

Recommendations	GR
Provide urinary drainage by either the suprapubic or urethral route.	A
Provide temporary 'damage control' measures in complex bladder injuries in the setting of polytrauma.	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 [256].

Recommendation	GR
Provide urgent urinary drainage by either the suprapubic or urethral route.	A

5.4.5 External genital injury

Traditionally, traumatic injuries of the external genitalia have a low priority and management is often deferred [392]. 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 [393].

Temporary damage control measures that might be applicable include:
• Compression dressing of the penis [182];
• 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 [394]. 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 [395, 396].

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 [397]. 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 unsurvivable or incompatible with survival in the home environment.

Triage sorts patients into four groups [398, 399]:
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.

5.5.3   ***Summary of evidence and recommendations for mass casualty events***

Summary of evidence	LE
Recent large scale military conflicts have raised the standard of practice for trauma patients.	4
The centralisation of trauma care and the establishment of trauma centres results in better outcomes for trauma patients.	3
Urologists have an important role to play in the management of polytrauma patients.	4

Recommendations	GR
Follow damage control principles in the management of unstable trauma patients.	A
Ensure that medical teams are well prepared to deal with polytrauma events.	A
Ensure that all surgical sub-specialists involved in trauma management are familiar with the principles of triage and damage control.	A

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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/guideline/urological-trauma/?type=panel. 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

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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 10 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.

Structure and scope
The panel wishes to take advantage of modern methods of delivering guideline information to clinicians dealing with these patients. We therefore plan to make a stepped information structure, in alignment with stepped care protocols. It is the vision of the panel to use new digital information sources like websites and apps to aid this process. Furthermore, the panel wishes to change the guideline according to the template used in all other non-oncology guidelines of the EAU. It has been 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.

Summary of Changes
For the 2016 version the panel has made updates focusing on two important changes to the guideline. The first one was to rewrite the guideline in such a way that it is centred around pain instead of being organ centred. Chapters in previous editions were named after the organ or after the specialist that is consulted by the patient. For the 2016 edition of this guideline, pain is the centre and all other information is built around this central theme. The guideline is partly theoretical to show the importance of using this pain centred approach. The biggest part, however, deals with the practical approach in diagnostics, treatment and management of patients with abdominal and pelvic pain. In this version the panel can only provide data on incidence, costs and quality of life issues in selected sub-chapters.

The second change the panel worked on is the way of presenting the practical aspects of pain. The guideline, based on pain in the centre, leads the healthcare professional through the different steps in the process of dealing with abdominal and pelvic pain patients. One could say that it is patient centred instead of complaint centred. Theoretical information will serve as background and can be read when needed.

This second focus of updating is of great importance for developing modern ways to make information available for the general clinicians who see the patient in their office. It contains red flags, associated conditions and available first line treatments. It is available for the medical specialist who sees a patient with chronic pain. The guideline highlights necessary investigations and phenotyping, treatment options, decision making on whether a treatment is rational or not, and how and when to refer to a specialised pelvic pain centre. Caregivers who treat patients for pain related problems like myofascial and sexological dysfunctions will find help in making treatment plans and in the timing of referring back to specialised pain care. The guideline will also aid those involved in coaching self-management and shared care.

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 the 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 guidelines [5].

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. These reference documents follow 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 Guidelines 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 three urologists, a neuro-urologist, two consultants in pain medicine, a gynaecologist, a psychologist, a gastroenterologist and one sexologist.

The Panel is most grateful for the expertise and support given by Dr. A. Cottrell (Guidelines Associate) in the process of transforming the document into the 2016 guideline structure, according to the template used in all other non-oncology guidelines of the EAU.

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 subdivided into that with primarily 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 subdivides 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 classification, 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 in 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
Subdividing pain syndromes
There is much debate on the subdivisions 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 thus be aimed at obtaining a differential diagnosis; repeated, unnecessary investigations are detrimental in the management of chronic pain syndromes.
2. A subdivision 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 autoimmune 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 the light of these and other publications, the symptom classification table has been updated (Table 1).

The debate in relation to subdividing 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. Whether this is appropriate, only time and good research will tell. 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	ONSET	Aching	UROLOGICAL	ANXIETY
Specific disease associated pelvic pain		Bladder	Inguinal	Acute	Burning	Frequency	About pain or putative cause of pain
OR		Scrotal	Urethral	Chronic	Stabbing	Nocturia	Catastrophic thinking about pain
Pelvic pain syndrome		Testicular	Penile/clitoral	ONGOING	Electric	Hesitance	DEPRESSION
		Epididymal	Perineal	Sporadic		Dysfunctional flow	Attributed to pain or impact of pain
		Penile	Rectal	Cyclical		Urge	Attributed to other causes
		Urethral	Back	Continuous		Incontinence	Unattributed
		Postvasectomy	Buttocks	TIME		GYNAECOLOGICAL	PTSD SYMPTOMS
	Gynaecological	Vulvar	Thighs	Filling		Menstrual	Re-experiencing
		Vestibular		Emptying		Menopause	Avoidance
		Clitoral		Immediate post		GASTROINTESTINAL	
		Endometriosis associated		Late post		Constipation	
		CPPS with cyclical exacerbations		TRIGGER		Diarrhoea	
		Dysmenorrhoea		Provoked		Bloatedness	
	Gastrointestinal	Irritable bowel		Spontaneous		Urge	
		Chronic anal				Incontinence	
		Intermittent chronic anal				NEUROLOGICAL	
	Peripheral nerves	Pudendal pain syndrome				Dysaesthesia	
	Sexological	Dyspareunia				Hyperaesthesia	
		Pelvic pain with sexual dysfunction				Allodynia	
	Psychological	Any pelvic organ				Hyperalegesie	
	Musculo-skeletal	Pelvic floor muscle				SEXUOLOGICAL	
		Abdominal muscle				Satisfaction	
		Spinal				Female dyspareunia	
		Coccyx				Sexual avoidance	
						Erectile dysfunction	
						Medication	
						MUSCLE	
						Function impairment	
						Fasciculation	
						CUTANEOUS	
						Trophic changes	
						Sensory changes	

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 10 years 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 the 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 6 months. That is, it can be cyclical over a 6-month period, such as the cyclical pain of dysmenorrhoea. Six months is arbitrary, however, it was chosen because 3 months was not considered long enough if we include cyclical pain conditions. 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 subdivided 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 CPPS.

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 subdivision 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. 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 subdivide by anatomy and prefer to refer to patients with pain perceived within the pelvis and no specific disease process as suffering from CPPS, subdivided 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 biopsychosocial 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 the 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 subdivision

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 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 subdivided 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: Urological pain syndromes

Urological Pain Syndromes	
Abdominal and Pelvic 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 prostadynia 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 subclassifications [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 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, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. 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 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, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. 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 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, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.
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 it is for that reason 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 subdivided 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 subdivided 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 preoccupation 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]: 3 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 (> 3 bowel movements per day or < 3 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 subgroup 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 overactivity 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.

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 is 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 and July 2011 and were restricted to English language publications.

Further updates of Chapter 5 'Gastrointestinal aspects of chronic pelvic pain' and Chapter 8 'Psychological aspects of chronic pelvic pain in the 2014 edition were based on systematic reviews of the literature in the aforementioned databases, including PsycInfo.

2.2 Review

This document was subject to peer review prior to publication in 2015. The decision to 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.

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 individual phenomena need to be addressed in their own right through multispecialty and multidisciplinary 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 done in 2004 [14] 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 in QOL
Assessing the quality of life in pelvic pain patients is challenging due to the multi-faceted nature of the complaints and the overlap between the different pelvic pain syndromes [15]. Assessment of quality of life is further complicated due to the complex pathology of pain itself [16].

Pelvic pain pain syndromes do have an impact on the QoL [17, 18]. This may result in depression, anxiety, impaired emotional functioning and fatigueness [18]. If these aspects are identified and targeted early in the diagnostic process, the associated pain symptoms may also improve [19]. Addressing co-morbidities will help in further improving the QoL [20]. QoL assessment is therefore important in patients with pelvic pain and should include physical, psychosocial and emotional tools, using standardised and validated instruments [17].

The impact of pain on QoL has been assessed in an extensive European study [14]. In-depth interviews with 4839 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 15 years, 21% had been diagnosed with depression because of their pain, 61% were less able or unable to work outside the home, 19% had lost their job and 13% had changed jobs because of their pain. 60% visited their doctor about their pain 2-9 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 somatic 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 may occur following such events and 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 [21]. Asking the patient about these events is important as they have an effect on a patient's psychological wellbeing [22-24].

Genetics also play a role in assessing the risk of developing chronic pain. An individual who has had one chronic pain syndrome is more likely to develop another. Family clusters of pain conditions are also observed and animals can be bred that are more prone to an apparent chronic pain state. A whole 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 development, environment and social factors also influence the situation. Evidence that BPS may have a

genetic component has been presented in several studies, but genetics may contribute to less than one third of total variation in susceptibility to BPS.

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. Symptom-related anxiety and central pain amplification may be measurably linked, as in IBS [25]. Central sensitisation has been demonstrated in symptomatic endometriosis [26]. Central changes are evident in association with dysmenorrhea and increasingly recognised as a risk for female pelvic pain [27]. 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. Women experiencing diagnoses which assign their pain to psychological origin, is common in primary care [28], due to scepticism about the reality or severity of their pain [29], thereby undermining any therapeutic relationship [30]. Division of aetiology into organic vs. psychogenic is unscientific. Pelvic pain and distress may be related [31]; the same is true of painful bladder and distress [32]. The only systematic review [33] 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 [34, 35]. In these studies it is suggested that there is increased frequency of sexual abuse or trauma history, anxiety and depression in women with CPP [36-40]. 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 [24] 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 [41]. Disentangling the influences and inferences requires further prospective studies or careful comparisons [21]. There is some evidence for a specific relationship between rape and CPP (and with fibromyalgia and functional gastrointestinal disorders) [42], recent sexual assault may prompt presentation of pelvic pain [34, 43]. 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 [42, 44]. 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 [45].

3.1.5.2   Underlying causes
The mechanisms that serve as an underlying cause for chronic pelvic pain are:

1.   Ongoing acute pain mechanisms [46] (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 [47-49].

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∂ 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, viscero-visceral, 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 [50-53]. However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in CPP in a small proportion of cases. 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, thus magnifying the afferent signalling. 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 signalling is often a trigger for the chronic pain mechanisms that maintain the perception of pain in the absence of ongoing peripheral pathology (see below) [54, 55].

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 stimulates the receptors of the transducers [56].
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 [57].

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 [58] 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 signalling 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 subthreshold and not usually perceived may be perceived. For instance, with central sensitisation, stimuli that are normally subthreshold may result in a sensation of fullness and a need to void or to defecate. Stimuli normally perceived 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 fibromyalgia.

It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain [59]. 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 [60].

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 [61] 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 [21] 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 [62], and interpreting absence of physical findings to indicate psychological origins of the complaint [63, 64]. 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 [65]. Better integration of sexology and mainstream psychology for pelvic pain in both men and women is needed [66], building on a

biopsychosocial formulation [67, 68].

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 [69]. 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 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 [63].

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 [21]. Anxiety and post-traumatic stress symptoms are common in some women with CPP [28, 70], 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 [71, 72], and anxiety often focuses on what might be 'wrong' [73]. 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, its implications, and its consequences for everyday life [74]. Reference to the studies of the IMMPACT group [75] 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 wellbeing [23, 24, 76].

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 onvergence-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 [51, 54, 77].

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 bilary colic, IBS, endometriosis, dysmenorrhoea, and recurrent bladder infection. 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 viscero-somatic neurones. 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 [78]. 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 [21].

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 [79, 80]. In the literature, numbers of the population-based prevalence of prostatitis symptoms range from 1 - 14.2% [81, 82]. 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 Bladder Pain Syndrome (BPS) prevalence have varied greatly, along with the diagnostic criteria and populations studied. Recent reports range from 0.06% to 30% [83-92]. There is a female predominance of about 10:1 [89, 93-95] but possibly no difference in race or ethnicity [79, 96, 97]. The relative proportions of classic and non-lesion disease are unclear. Incidence in studies has ranged from 5 to 50% [98-102]. There is increasing evidence that children under 18 may also be affected, although prevalence figures are low thus, BPS cannot be excluded on the basis of age [103].

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 [104, 105]. 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 the evaluation tools and populations [106, 107]. ED was prevalent in 27.4% of Italian men aged 25-50 [108], 15.2% among Turkish men (significantly higher than in the control group) [109] and 43% among Finnish men with PPS [110]. 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 [111, 112]. Recently, a significant correlation between "chronic prostatitis", CPP symptoms (measured by NIH-CPSI) and ED (measured by IIEF) was confirmed [113], while other studies using the same questionnaires were not able to confirm such a correlation [68, 114]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [106, 107, 115, 116].

In community-based studies in the UK [117], New Zealand [118] and Australia [119], 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 [120, 121]. 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 [120]. In line with the results of the community based studies, patients with CPP reported more sexual problems such as dyspareunia, problems with desire or arousal and lubrication than women without CPP [120, 122, 123]. One study of patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems [124].

3.2.2.4 Myofascial pain syndromes
The relationship between muscular dysfunction (especially overactivity) and pelvic pain has been found in several studies. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles [125]. 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) [126]. This relationship has been found in chronic prostatitis [127] BPS [128] and vulvar pain [129]. 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 in QoL
Data on the influence in 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 [130] is that the condition probably occurs in susceptible men exposed to one or more initiating factor, 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 [130]. 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.

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 [131]. Experimental induction of CPP by O-antigen deficient bacterial strains reinstates the bacterial hypothesis [132]. Pancystitis, with associated perineural inflammatory infiltrates, and mast cell count increase is an essential part of BPS type 3 C [133], but is scant in non-lesion BPS [24, 60, 134, 135]. 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 [136-143] and a consequent cytotoxic effect [144, 145].

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 [146-152].

Risk of BPS correlates with a number of non-bladder syndromes in each patient [153]. 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 [154].

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 pundendal nerves innervate the scrotum [155]. Any pathology or intervention at the origin or along the course of the nerves may result in pain perceived in the scrotum [156].

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 [157]. In men with post-vasectomy pain, 2-6% have a VAS score > 5 [158]. In a large cohort study of 625 men, the likelihood of scrotal pain after 6 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%) [159].

The second 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 [156, 160]. In one particular study, there was no difference at 1 year but after 5 years, the open group had far fewer patients with scrotal pain [161].

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 is used to support the theory of epithelial leakage [162, 163]. Another possible mechanism is neuropathic hypersensitivity following urinary tract infection [164]. The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multiparity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis [165].

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 > 6 months, it can be diagnosed as vulvar pain syndrome previously known as "vulvodynia" or "chronic vaginal" 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 vulvodynia 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 postoperative scarring may result in nerve injury [166].

Pudendal neuralgia is the most often mentioned form of nerve damage in the literature. Anatomical variations may predispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) [167, 168].
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/sacrotuberous 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 [169-171]. 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 [172, 173]. 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 [174, 175]. 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 presacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer [176].
- 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 [177].
- Child birth and repeated abdominal straining associated with chronic constipation [178] are thought to predispose 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 [124]. 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 (SSRI) can also decrease libido [179] 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 the present, the most commonly used tool is the International Index of Erectile Function (IIEF) questionnaire [114].

The presence of pelvic pain may increase the risk for ED independent of age [180, 181]. On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation [105]. 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 [116]. These arguments are important for the understanding of the close relationship between CPP symptoms, disturbed sexuality, impact on QoL, and psychological implications including depression [104-107, 182]. 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 [104, 181]. PPS patients reported greater sexual and relationship problems [104, 181, 183]. On the other hand, it was found that men with PPS did not report significantly decreased sexual satisfaction compared to controls [184]. There is consensus that therapeutic strategies reducing symptoms of pelvic pain, are of relevance in relation to changes of sexuality. 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 [118, 185-187]. 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" [188]. 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 [189]. Patients with CPP reported more sexual problems than women with any other type of chronic pain problem [190]. The quality of intimate relationships is closely connected with sexual function [191]. Satisfaction with sexual relationships appears to be associated with higher marital functioning [192]. 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 [192].

Approximately two-thirds of patients in another study have reported reduced frequency in their sexual

relations as a result of CPP [193]. 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 sexual dysfunction [194]. 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 [180]. In a study in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain [124]. The Female Sexual Function Index (FSFI) has been developed as a brief, multidimensional 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 did 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 [36].

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 [195]. Muscle relaxation can diminish spasm and pain [196]. 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 [127].

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 [470]. 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 [197].

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 ileopsoas 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 Zondovan was 1.58/1000.

3.3.2 Prevalence
Using a vague definition of continuous or episodic pain over 6 months situated below the umbilicus one study reported that CPP was the one of most common diagnosis in primary care units in Great Britain [198]. The monthly prevalence rate of CPP in this study was 21.5/1000, with an annual prevalence of 38.3/1000. They increase significantly with older age and vary significantly between regions in the UK. The overall prevalence of anorectal pain in a sample of US householders was 6.6% and was more common in women [199]. IBS is associated with common gynaecologic problems (endometriosis, dyspareunia, and dysmenorrhea) [200]. 50% of women who presented with abdominal pain to the gynaecologic clinic or were scheduled for laparoscopy due to CPP had symptoms of IBS [201]. In a survey from Olmsted county 20 % of women reported CPP and 40% of those met criteria for IBS [202]. 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 [203]. 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 in 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 is 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 [204]. Subgroups of IBS with predominance of diarrhea or constipation show no difference in HRQoL. Multivariate 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 absenteism from work. The annual costs to society can be calculated by using the average population earnings. In Germany direct care costs are estimated € 791 and societal costs € 995 per patient with IBS per year which may be comparable to patients with CPP [205].

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 multispecialty and multidisciplinary care.	2

Recommendations	GR
All of those involved in the management of CPP should have knowledge of peripheral and central pain mechanisms.	A
The early assessment of patients with CPP should involve: • 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 multispecialty and multidisciplinary environment with consideration of all their symptoms.	A

CPP = chronic pelvic pain; CPPS = chronic pelvic pain syndrome.

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 3 out of the past 6 months. This implies that specific disease-associated pelvic pain caused by bacterial infection, cancer, 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 [206-208].

Anxiety about pain often refers to fears of missed pathology (particularly cancer) as the cause of pain, or to uncertainties about treatment and prognosis. The question: "What do you believe or fear is the cause of your pain?" has been suggested [209]. Anxiety may also concern urinary urgency and frequency as a possible problem in social settings.

Depression or depressed mood are common in chronic pain [e.g [210], 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, is available [211]. Generic quality of life measures are helpful. If such an instrument is not already used in the clinic, the Brief Pain Inventory [212] provides a broad and economical assessment of interference of pain with various aspects of life in various languages. (For further suggested instruments see [213]). In a study, more pain, pain-contingent rest, and urinary symptoms were associated with poorer function [49].

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
PPS 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 3 out of the past 6 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 [41]. 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
BPS 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 [214-218].
4.   Aggravated by food or drink [218].
BPS 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 3 months with symptom onset at least 6 months before diagnosis [219].

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 within 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 that 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 the visceral and muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dispareunia, 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 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 chronic pelvic pain syndromes, 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 bulbocavernosa reflex in the male may also provide useful information concerning the intactness of the pudendal nerves. Clinical pelvic examination should be a single digit examination if possible. The usual bimanual examination can generate severe pain so the examiner must proceed with caution. A rectal examination is done to look for prostate abnormalities in male patients including pain on palpation and to examine the rectum and the pelvic floor muscles regarding muscle tenderness and trigger points.

At clinical examination, perianal dermatitis may be found as a sign of faecal incontinence or diarrhoea. Fissures may be easily overlooked and should be search for thoroughly in patients with anal pain. Rectal digital examination findings may show high or low anal sphincter resting pressure, a tender puborectalis muscle in patients with the Levator Ani Syndrome, and occasionally increased perineal descent. The tenderness during posterior traction on the puborectalis muscle differentiates between Levator Ani Syndrome and Unspecified

Functional Anorectal Pain and is used in most studies as the main inclusion criterion. Dyssynergic (paradoxical) contraction of the pelvic muscles when instructed to strain during defecation is a frequent finding in patients with pelvic pain. Attention should be paid to anal or rectal prolapse at straining, and ideally during combined rectal and vaginal examination to diagnose pelvic organ prolapse.

A full clinical examination of the spinal, muscular, nervous and urogenital systems is necessary to aid in diagnosis of pudendal neuralgia, especially to detect signs indicating another pathology. Often, there is little to find in pudendal neuralgia and frequently findings are non-specific. The main pathognomonic features are the signs of nerve injury in the appropriate neurological distribution, for example, allodynia or numbness. Tenderness in response to pressure over the pudendal nerve may aid the clinical diagnosis. This may be elicited by per rectal or per vaginal examination and palpation in the region of the ischeal spine and/or Alcock's canal. Muscle tenderness and the presence of trigger points in the muscles may confuse the picture. Trigger points may be present in a range of muscles, both within the pelvis (levator ani and obturator internus muscles) or externally (e.g., the piriformis, adductors, rectus abdominus or paraspinal muscles).

4.2   Supplemental evaluation

If history is suggestive of lower urinary tract, gynaecological, anorectal or other known etiology disease diagnostic workup should follow respective guidelines.

4.2.1   *Assessing pain and related symptoms*
Determination of the severity of disease, its progression and treatment response can be assessed only by means of a reliable symptom-scoring instrument. These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients. Pain should always be assessed (see below) to identify progression and treatment response. As well as doing this in the clinic, the patient can keep a daily record (pain diary). This may need to include other relevant variables such as voiding, sexual activity, activity levels, or analgesic use.

Increased attention to patient reported outcomes gives prominence to patients' views on their disease and pain diaries, in patients' own environments, improve data quality.

QoL should also be measured because it can be very poor compared to other chronic diseases [42, 43]. In a study [49] more pain, pain-contingent rest, and urinary symptoms were associated with greater disability (also measured by self-report), and pain was predicted by depression and by catastrophising (helplessness subscale).

Where the primary outcome of treatment is pain relief, it is useful before starting treatment to agree a clinically useful level of relief (see [220]). The most reliable methods are:

A 5 point verbal scale: none, mild, moderate, severe, very severe pain
A VAS score from 1 to 10

0	1	2	3	4	5	6	7	8	9	10
no pain										extreme pain
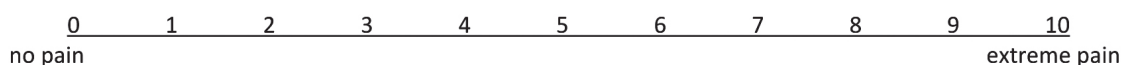
Pain assessment ratings are not independent of cognitive and emotional variables [10]. Target outcomes of pain severity, distress and disability co-vary only partly, and improvement in one does not necessarily imply improvement in the others. When the primary outcome is pain its meaning should be anchored in discussion of clinically important difference (e.g. see [220].

Prostate pain syndrome
Reliable, valid indices of symptoms and QoL are the NIH-CPSI [221] and the International Prostate Symptom Score (I-PSS) [222].

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 [223].

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 [224, 225]. 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 disfunction 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" [188]. The female sexual function index (FSFI) has been developed as a brief, multidimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain.

4.2.2   *Focused myofascial evaluation*
Pelvic floor muscle testing can be done by the medical doctor but a consultation of the pelvic floor 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 [226]. Rectal examination is a good way to test the pelvic floor function in men [227]. 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%) [228].

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 [229-239]. Infiltration at the ischeal 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 ultrasound (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 bulbocavernosal reflex [305, 312, 317-319]. 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
MR neurography has been increasingly used in specialised centers for the diagnosis of 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
MRI 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 hereby reduce the sensitivity of the method, underestimating the size of entero- and rectoceles as well as the amount of interception.

4.2.5   ***Laboratory Tests***

Microbiology tests
Prostate pain syndrome
Laboratory diagnosis has been classically based on the four-glass test for bacterial localisation [240]. Besides sterile pre-massage urine (voided bladder urine-2), PPS shows < 10,000 cfu 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) [241-243]. 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 [244].

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 meaurement: barostat) may be useful to diagnose dyssynergic defaecation and hypersensitivity of the rectum which are typical for patients with chronic pelvic pain and IBS. Flexible rectosigmoidoscopy or colonoscopy should be considered in patients with anorectal pain according to performed to rule out coincidental colorectal pathology.

Laparoscopy for females
Laparoscopy is perhaps the most useful invasive investigation to exclude gynaecological pathology [245, 246] and to assist in the differential diagnosis of CPP in women [247]. Often, it is combined with cystoscopy [248, 249] 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 [250], although showing women the photograph of their pelvic contents did not improve on explanation alone [251]; and integrating somatic and psychological assessment from the start rather than dealing with psychological concerns only after excluding organic causes of pelvic pain [252].

Cystoscopy and bladder biopsy
Despite controversy on the diagnostic and follow-up value of cystoscopy in BPS [253-257], 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 [258]). 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 [217]. The scar ruptures with increasing bladder distension, producing a characteristic water fall type of bleeding. There is a strong association between BPS type 3 and reduced bladder capacity under anaesthesia [259]. 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 [260]. Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease [137, 162, 258, 261, 262]. 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

[a]*Cystoscopy: glomerulations grade 2-3*
[b]*Lesion per Fall's definition with/without glomerulations*
[c]*Histology 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
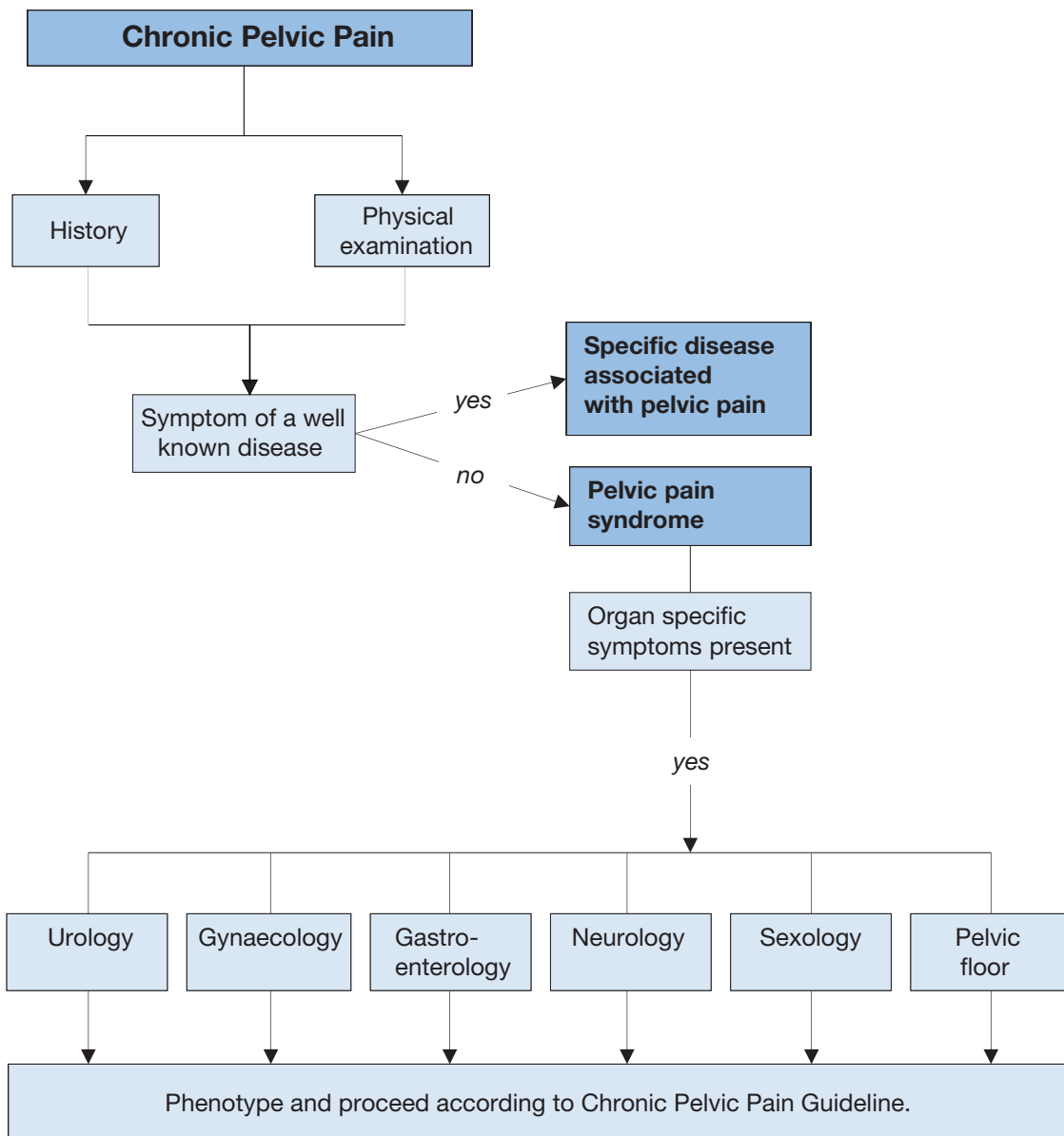
Figure 2: Phenotyping of pelvic pain - UPOINT classification

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

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 [247]. Secondary dysmenorrhoea suggests the development of a pathological process, such as endometriosis [246], adenomyosis [263] or pelvic infection, which need to be excluded.

Infection
In premenopausal 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 [264], as they can cause severe pelvic/vaginal/vulvar pain [265] and are associated with ulcerating lesions and inflammation, which may lead to urinary retention [266]. If there is any doubt about the diagnosis, laparoscopy may be helpful, as one of the differential diagnosis is endometriosis.

Endometriosis and adenomyosis
The incidence of endometriosis is rising in the developed world. The precise aetiology is unknown, but an association with nulliparity is well known. 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 [267-269].
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 [270].

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 [271]. There is often a transient problem with oestrogen deficiency in the postpartum 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 [272]. 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") [273-275]. Although they may have a role in supporting the vagina, they are also associated with several complications including bladder, bowel and vaginal trauma [274]. In a subset of these patients, chronic pain may ensue, because mesh insertion may cause nerve and muscle irritation [271]. 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 anticoagulation 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 6 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 [276, 277].

4.5 Summary of evidence and recommendations: diagnostic evaluation

4.5.1 Diagnostic evaluation of PPS

Summary of evidence	LE
PPS is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.	2b
PPS has no known single aetiology.	3
Pain in PPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
PPS 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 NIH-CPSI, 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 quality of life.	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 ESSIC guidelines	A
After primary exclusion of specific diseases, patients with symptoms according to the above definition should be diagnosed with 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

BPS = Bladder pain syndrome.

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 content does not aid in diagnostics 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 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 multidisciplinary team environment.	B
Imaging and neurophysiology helps 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 biopsychosocial model should be applied in the evaluation of the effect of chronic pelvic pain syndrome on the sexual function of the patient.	B
The biopsychosocial model should be incorporated in research in 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 reassure 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
Overactivity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a
Overactivity 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 biopsychosocial 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 [278]. 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 [279].

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 nonpainful 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 [280]. They found 6 RCT's 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 1 year follow-up of 64%.

This approach consists of myofascial relaxation and tension, improving posture and movement in combination with CBT [281].

Pelvic floor muscle pain
Treating pelvic floor overactivity 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 [282].

Myofacial trigger point release (MTrP's)
Treatment of MTrP's 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 [283]. 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 [284]. Other reviews have concluded that the same is true for the difference between dry and wet needling [285, 286].

Physiotherapy in BPS
General muscular exercise may be beneficial in some BPS patients [287]. 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 [288]. The role of specific levator ani trigger point injections in women with CPP has been studied [289]. 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; 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 [290a].

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 [290b]. 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 12 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 [125]. 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 [291]. 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 postcoital flares.

Other behavioural changes involve pre- and postcoital voiding, application of ice packs to the genital or suprapubic area [291, 292], 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, urethra, and vaginal friction, and women with signs of vulvovaginal atrophy may benefit from introital application of minimally absorbed locally applied oestrogen cream [293]. In patients with an overactive pelvic floor, referral for physical therapy, myofascial release, and internal pelvic floor muscle massage may offer relief [294].

Other physical therapy interventions
Electromagnetic therapy in a small, sham-controlled, double-blind study of four weeks showed a significant, sustained effect over a 1-year period for CPPS [295].
In uncontrolled studies significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy [296, 297].

A small sham-controlled double-blind study of four times weekly perineal extracorporeal shock wave 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 12 weeks [298]. Confirmatory studies are awaited because of an absent placebo-effect, which is very unusual in PPS trials.

In a small three-arm randomised trial of CPPS in men, electroacupuncture was superior to sham treatment and advice and exercise alone [299]. In a recent prospective case series of six weeks of weekly electro-acupuncture of 97 patients with PPS, 92% showed significant improvement in total NIH-CPSI score. Based on these studies, no definitive conclusion can be drawn.

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 [300]. 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 [509]. 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 [301, 302], but these have been neglected in pelvic pain. A recent Cochrane systematic review and meta-analysis of non-surgical treatments for pelvic pain [303], excluding endometriosis, IBS, and chronic PID [304] found five eligible trials of psychologically-based treatment, but they were diverse and not combined for analysis. Surprisingly, the single component treatments for chronic pelvic pain, counselling about ultrasound results [305], and emotional disclosure [306], showed improvements in pain, while three more standard multicomponent (including psychological) treatments for pain [252, 281, 307] did not. Pain relief, of around 50%, is comparable to that from pharmacotherapy, but follow-up is lacking. Only two of the five RCTs measured mood improvement, and found no effects of psychological and physiotherapeutic treatment over gynaecological consultation [281], or for writing with vs. without disclosure of distress [306]. The importance of multidisciplinary treatment is emphasised by several reviews [308, 309], and the need for high quality psychological treatment evaluation is underlined [308]. For less disabled and distressed patients, this can be delivered in part over the internet [310]. Several other reviews make positive comments on psychological involvement [311], and recommend addressing psychological concerns from the outset, directed at the pain itself, with the intended outcome of reducing its impact on life [25], or at adjustment to pain, with improved mood and function and reduced health care use, with or without pain reduction [26].

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 [316]. Monotherapeutic strategies for the treatment of PPS may fail [317], therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past 10 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 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 [318]. In a recent meta-analysis, two studies of NSAIDs [244, 318] and one with prednisolone [319] 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.

Alpha-blockers
Positive results from RCTs of alpha-blockers, i.e. terazosin [320, 321], alfuzosin [322], doxazosin [323, 324], tamsulosin [325, 326], and silodosin [327] have led to widespread use of alpha-antagonists in the treatment of PPS in recent years. The most recent systematic review and network meta-analyses of alpha-blockers [328] have 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 perceptive or significant improvement, may be lower than expected from the change in mean symptom scores. Overall, alpha-blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPS patients [329]. 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 4-6 weeks or even longer. Unfortunately, culture, leukocyte and antibody status of prostate-specific specimens does not predict antibiotic response in patients with PPS [330], and prostate biopsy culture findings do not differ from those of healthy controls [331]. The only randomised placebo-controlled trials of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (6 weeks) [130], levofloxacin (6 weeks) [332], and tetracycline hydrochloride (12 weeks) [333]. The studies have been analysed in a recently published meta-analyses [328, 334]. 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 alpha-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 [334]. 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 6 weeks.

5-alpha-reductase inhibitors
Although a few small pilot studies with 5-alpha-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 [335]. In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a 1-year period, but lacked a placebo-control arm [336]. A 6-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because

of a lack of statistical power [337]. In a recently published study, NIH-CPSI scores decreased significantly in a subgroup of men enrolled in a prostate cancer risk reduction study treated with dutasteride compared to placebo [338]. 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-alpha-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 [338].

Phytotherapy
Phytotherapy applies scientific research to the practice of herbal medicine. An adequately powered placebo-controlled RCT of Cernilton, showed clinically significant symptom improvement over a 12-week period in inflammatory PPS patients (NIH Cat. IIIA) [339]. The effect was mainly based on a significant effect on pain. Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT [340]. In contrast, treatment with saw palmetto, most commonly used for benign prostatic hyperplasia, did not improve symptoms over a 1-year period [336]. In a systematic review and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo [328]. In addition, overall response rate in network analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1-1.6).

Pregabalin is an antiepileptic 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 [341], a 6-week course of pregabalin (n = 218) compared to placebo (n = 106) did not result in a significant reduction of NIH-CPSI total score [342].

Pentosan polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. One study using oral high-dose (3x 300 mg/day) demonstrates a significant improvement in clinical global assessment and QoL over placebo in men with PPS, suggesting a possible common aetiology [343].

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 (tiocolchicoside), an anti-inflammatory drug (ibuprofen) and an alpha-blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an alpha-blocker alone [324].

Botulinum toxin in a small randomised placebo-controlled study of perineal skeletal muscle injection (100 U) showed some effect in the global response assessment and the NIH-CPSI pain subdomain score. However, patient numbers were low (13 in the botulinum toxin type A (BTX-A) group and 16 in the placebo group), and follow-up too short to draw definitive conclusions. Side-effects are unclear.

Zafirlukast, a leukotriene antagonist, and prednisone in two low-power placebo-controlled studies failed to show a benefit [319, 344]. 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 [345].

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 [346, 347].

<u>**Bladder Pain Syndrome**</u>

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 [348] and H2 [349] receptor subtypes, with variable results. A prospective placebo-controlled RCT of hydroxyzine or sodium pentosan polysulphate did not show a significant effect [350].

Amitriptyline
Amitriptyline is a tricyclic antidepressant. Several reports have indicated improvement of BPS symptoms after

oral amitriptyline [94, 351, 352]. Amitriptyline has been shown to be beneficial when compared with placebo plus behavioural modification [353]. Drowsiness is a limiting factor with amitriptyline, nortriptyline is sometimes considered instead.

Pentosan polysulphate sodium Is a semi-synthetic drug manufactured from beech-wood hemicellulose. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported [354, 355]. Pentosan polysulphate sodium had a more favourable effect in BPS type 3C than in non-lesion disease [356]. 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 pentosan polysulphate sodium, additional subcutaneous heparin was helpful [357].

Immunosuppressants

Azathioprine treatment has resulted in disappearance of pain and urinary frequency [358]. Initial evaluation of cyclosporin A (CyA) [359] and methotrexate [360] 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 drugs are administered due to poor oral bioavailability 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.

Local anaesthetics

There are sporadic reports of successful treatment of BPS with intravesical lidocaine [361, 362]. Alkalisation of lidocaine improves its pharmacokinetics [363]. Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after 2 weeks in 80% [364]. Intravesical instillation of alkalinised lidocaine or placebo for five consecutive days resulted in significantly sustained symptom relief for up to 1 month [365].

Hyaluronic acid and chondroitin sulphate are described to repair defects in the GAG layer. Despite the fact that intravesical GAG replenishment has been in use for about 20 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, and concentrations. More important, there are differences in proven efficacy. Only for chondroitin sulphate, a combination containing chondroitin sulfate and hyaluronic acid and pentosan polysulphate RCTs are published. 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 [366].

Intravesical heparin

BPS patients were treated with heparin for three months, and over half had control of symptoms, with continued improvement after 1 year of therapy [367]. 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 [368]. 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 2 and 12 months [369].

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 [370].

Treatments of limited value for BPS

Cimetidine

There is limited data to suggest that Cimetidine improves symptoms of BPS in the short-term [371]. Compared with placebo for 3 months, cimetidine significantly improved symptom scores, pain and nocturia, although the bladder mucosa showed no histological changes in either group [372].

Prostaglandins

Misoprostol is a prostaglandin that regulates various immunological cascades. After three months of treatment with misoprostol, 14/25 patients had significantly improved, with 12 showing a sustained response after a further six months [373]. 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 [121, 374, 375]. NO is elevated in patients with BPS [376]. However, others have not demonstrated symptomatic relief or changes in NO production after treatment [377, 378].

Oxybutynin is an anticholinergic drug used in overactive detrusor dysfunction. Intravesical oxybutynin combined with bladder training improves functional bladder capacity, volume at first sensation, and cystometric bladder capacity [379]. However, an effect on pain has not been reported.

Duloxetine (a serotonin-norepinephrine reuptake inhibitor antidepressant with a licence for the management of neuropathic pain) did not significantly improve symptoms of BPS [380]. 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 [381-385]. Due to high complication rates, clorpactin instillations can no longer be recommended [381, 382, 384, 386, 387].

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 [388]

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 [303].

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 my be 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. Thier effectiveness as contraceptives range from 92-99.9% [312]. The precise mechanism of intrauterine contraceptive devices is unclear. Current evidence indicates they exert their primary effect before fertilization, reducing the opportunity of sperm to fertilize an ovum.Thier efficacy approaches 99% [313].

Gonadotropin-releasing hormone (GnRH) bind to specific receptors on pituitary gonadotrophs. Prolonged activation of GnRH receptors by GnRH leads to desensitization and consequently to suppressed gonadotrophin secretion. By contrast, GnRH antagonists compete with GnRH for receptors on gonadotroph 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 redcuing the size of fibroids, endometrial bleeding and endometriosis [314].

Pelvic Floor and Chronic Anal Pain
Botulinum A toxin (pelvic floor)
Botulinum A toxin (BTX-A) has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective [389]. Reviews do not support the injection of BTX-A into trigger points [390]. Pelvic floor muscle overactivity 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 [391]. BTX-A can also be injected at the sphincter level to improve urination or defecation. Relaxation of the urethral sphincter alleviates the bladder problems and secondarily the spasm. In a cohort study of 13 patients with CPP, BTX-A was injected into the external urethral sphincter. Subjectively, 11 patients reported a substantial change in pain symptoms, from 7.2 to 1.6 on a VAS [392].

Botulinum A toxin (chronic anal pain syndrome)
CPP associated with spasm of the levator ani muscles and 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 overactivity of the pelvic floor muscles, defined as a vaginal resting pressure > 40 cm H_2O. Although dyspareunia and dysmenorrhea improved, non-menstrual pelvic pain scores were not significantly altered [393]. 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 H_2O) 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 for reducing pelvic floor-muscle associated pain with acceptable adverse effects such as occasional urinary and faecal stress incontinence [391]. However, recently, a small RCT failed to show any benefit of BTX-A [394].

<u>Intermittent chronic anal pain syndrome</u>
Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled beta-2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration [395]. Other treatment options are topic diltiazem and BTX-A [396]. However, there is still some controversy as regards 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.

5.2.2   Analgesics
If the use of simple analgesics fails to provide adequate benefit, then consider using the neuropathic agents, 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 chapters. The management requires a holistic approach with biological, psychological and social components. Few studies have specifically looked at medications used in CPP [304], therefore, a wider look at the literature has been undertaken, 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 to provide benefit does not mean that there is 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 drugs 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 [397]. It is often available over the counter without prescription. There is evidence that paracetamol is beneficial in managing somatic and arthritic pain [398]

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 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 [399], 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 [315], 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 [400]. 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 (TCA's) have multiple mechanisms of action including, blockade of acetylcholine receptors, inhibition of serotonin and noradrenalin re-uptake, and blockade of histamine H1 receptors. It also have anxiolytic affects [401] and are frequently limited by their side-effects. TCA's have a long history of use in pain medicine and have been subjected to a Cochrane review [402], 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 [493]. Nortriptyline and imipramine are used as alternatives.

Other Antidepressants

Duloxetine is a serotonin-norepinephrine 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 [403]. Side-effects are common and may result in its discontinuation.

Selective serotonin reuptake inhibitors (SSRIs) 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 [402-404].

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 [400].
Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit [405]. 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 [406]. It provides good quality relief with NNT of approximately six. Side-effects are common, notably drowsiness, dizziness and peripheral oedema. For upper 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 then amitriptyline alone [407].

Pregabalin is a commonly used neuromodulator with good evidence of efficacy in some neuropathic conditions but the NNT varies depending on the condition [408]. 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. As with gabapentin, side-effects are relatively common and may not be tolerated by patients. 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 analgesia [409]. 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 [410]. There is also information available online for patients [411, 412]. 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 [413, 414]. 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 3 days to 1 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., iliostomy). 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 [415].

Oxycodone may have greater efficacy than morphine in some situations, such as hyperalgesic states including visceral pain [416].

Tramadol is an established analgesic with dual effects on opioid receptors and serotonin release. More recently, tapentadol, has been released with opioid action and noradrenalin 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 A (BTX-A)
BTX-A may have an antinociceptive effect on bladder afferent pathways, producing symptomatic and urodynamic improvements [102]. Treatment with hydrodistension and hydrodistension plus intravesical BTX-A has been compared [417]. There was symptomatic improvement in all patients. However, in the hydrodistension only group, 70% returned to their previous symptoms after 1 month, while in the BTX-A-treated patients, VAS score, and functional and cystometric bladder capacity improved at 3 months.
BTX-A trigonal-only injection seems effective and long-lasting as 87% of patients reported improvement after 3 months follow-up [418]. Over 50% reported continued benefit 9 months after the first treatment. When retreatment was needed, similar results were obtained. The authors concluded that this treatment is safe, effective and can be repeated.

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 3 years [419, 420]. Prolonged amelioration of pain and urgency has been described for transurethral laser ablation as well [421].

Open Surgery for BPS
BPS is benign and does not shorten life, thus operative procedures rank last in the therapeutic algorithm. There is no evidence 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 preoperative evaluation, with an emphasis on determining the relevant disease location and subtype. If surgery is considered, our advice is to refer the patient to a specialist center experienced in managing CPP with a multidisciplinary 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 [422]. Reports that unresected BPS bladders cease to induce symptoms after loss of contact with urine are scarce [99, 423].

2. Supratrigonal cystectomy with subsequent bladder augmentation represents the most favoured continence-preserving surgical technique. Various intestinal segments have been used for trigonal augmentation [424-426].

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 in 50% of patients and blamed surgical failure on the trigone left in place [427]. In contrast, Another study [428] reported six out of 17 patients being completely cured by supratrigonal resection [427]. 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 [429].

4. Cystectomy with formation of an ileal conduit still ranks first in current USA practice trends for BPS surgery [430]. 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 [431]. It is important to note that pregnancies with subsequent lower-segment Caesarean section have been reported after ileocystoplasty [431, 432].

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.

Urethral Pain Syndrome
There is no specific treatment that can be advised. Management should be multidisciplinary and multimodal [433]. 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 [434]. The majority of publications on treatment of urethral pain syndrome have come from psychologists [164].

Presumed intra-abdominal adhesions
In gynaeocological patients with CPP and presumed adhesions, there is no consensus as to whether adhesiolysis should be performed to improve pain [435, 436].

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 in the removal of early extensive endometriosis compared to sham surgery [437, 438].

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 [171, 231, 439-443]. Currently, there has been only one prospective randomised study [441]. This study suggests that, if the patient has had the pain for < 6 years, 66% of patients will see some improvement with surgery (compared to 40% if the pain has been present for > 6 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 [444]. 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 [445]. 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 [446]. Long-term results were verified in a retrospective study of patients from 1994 to 2008 [447]. Permanent SNM implantation was performed in patients who showed at least 50% improvement in symptoms with a temporary peripheral nerve evaluation test [447]. 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-/postoperative pelvic pain and urgency/frequency scores were 21.61 ± 8.6/9.22 ± 6.6, and mean pre-/postoperative visual analogue pain scale (VAPS) scores were 6.5 ± 2.9/2.4 ± 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 multidisciplinary care [449-452].

Chronic Anal Pain Syndrome

Sacral neuromodulation and percutaneous tibial nerve stimulation in pelvic pain. 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 3 patients (2 improved) while biofeedback was the most used modality with the greatest treatment effect in patients with defecatory dysfunction (29 patients, 17 improved) [396]. Sacral neuromodulation has been reported to be somewhat beneficial in two uncontrolled studies, showing improvement in about half the patients [453, 454]. Sacral neuromodulation may be a choice in patients with CPP who failed to respond to biofeedback and drug therapy. The less invasive percutaneous tibial nerve stimulation (PTNS) was tested in 12 women with CPP lasting for at least 6 months and showed an improvement in pain, QoL and sexual life [455]. 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 [51]. 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 sight 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 [456]. 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 [229-239].

Infiltration at the ischeal 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 radiofrequency stimulation has also been suggested as a treatment [457].

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
Alpha-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
Pentosan 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 may have a modest effect in PPS.	2b
Posterior tibial nerve stimulation is probably effective for the treatment of PPS.	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 PPS.	A
Single use of antimicrobial therapy (quinolones or tetracyclines) is recommended in treatment-naïve patients over a minimum of 6 weeks with a duration of PPS < 1 year.	A
Alpha-blockers are recommended for patients with a duration of PPS < 1 year.	A
High-dose pentosan polysulphate is recommended in PPS.	A
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

PPS = prostate pain syndrome; NSAIDs = non-steroidal anti-inflammatory drugs.

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 pentosanpolysulphate sodium is effective for pain and related symptoms of BPS.	1a
Oral pentosanpolysulphate sodium plus subcutaneous heparin is effective for pain and related symptoms of BPS, especially in initially low responders to pentosanpolysulphate sodium alone.	1b
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical pentosanpolysulphate sodium 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 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 for cystectomy for BPS is variable.	3

Recommendations	GR
Offer subtype and phenotype-oriented therapy for the treatment of 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 pentosanpolysulphate sodium for the treatment of BPS.	A
Treatment with oral pentosanpolysulphate sodium plus subcutaneous heparin is recommended especially in low responders to pentosanpolysulphate sodium alone.	A
Administer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	A
Administer intravesical pentosanpolysulphate sodium before more invasive treatment alone or combined with oral pentosanpolysulphate sodium.	A
Administer submucosal injection of BTX-A plus hydrodistension if intravesical instillation therapies have failed.	A
All ablative organ surgery should be the last resort for 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

DMSO = dimethyl sulphoxide; BPS = bladder pain syndrome; BTX-A = Botulinum A toxin;
BCG = Bacillus Calmette Guérin.

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 multidisciplinary and multimodal 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 multidisciplinary 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 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
Biofeedback treatment is recommended in patients with pelvic pain and dyssynergic defecation.	A
Offer botulinum toxin 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, biofeedback 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.	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. 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 where 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 patients, 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 country based. This does not facilitate easy referral schemes. It is advised that patients are referred to a centre that is working with a multidisciplinary 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 life activities in all domains of life. Self-help programs maybe advised and can be of help. This 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 patients feels the same pain again it helps to start at an early stage with the self-management strategies that he has learned during the former treatment. By doing so they will have the best chance of preventing the development of pelvic pain syndromes again.

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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. 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 Reporting and Grading of Complications after Urologic Surgical Procedures

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European Association of Urology

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1. INTRODUCTION

Evidence of variations in clinical practice, together with rising costs associated with constrained resources in most health care systems over the past decade, has triggered growing interest in evaluating the quality of our surgical work [1-3]. At present, the main methods of assessing surgical results for audit and quality assurance remain mortality and morbidity [4-6]. Thus measurement of morbidity requires an accurate definition of a surgical complication. Although the incidence of postoperative complications is still the most frequently used surrogate marker of quality in surgery [1, 3, 7], the direct cause-and-effect relationship between surgery and complications is often difficult to assess. This uncertainty carries a risk of underreporting surgical complications, with substantial consequences.

Most published articles focus only on positive outcomes (e.g. trifecta in prostate cancer after radical prostatectomy) [8]. There is a need to compare complications for each specific approach in a systematic, objective, and reproducible way. As yet, no definitions for complications or guidelines for reporting surgical outcomes have been universally accepted. Reporting and grading of complications in a structured fashion is only one aspect of the quality of outcome reporting. In 2002, Martin *et al.* proposed 10 criteria that should be met when reporting complications following surgery [9] (Table 1). Clavien and Dindo proposed a system for grading the severity of postoperative complications [10] that was subsequently revised and validated [11] (Table 2).

Table 1: Martin *et al.* criteria of accurate and comprehensive reporting of surgical complications [9]

Criteria	Requirement
Method of accruing data defined	Prospective or retrospective accrual of data are indicated
Duration of follow-up indicated	Report clarifies the time period of postoperative accrual of complications such as 30 days or same hospitalisation
Outpatient information included	Study indicates that complications first identified following discharge are included in the analysis
Definition of complications provided	Article defines at least one complication with specific inclusion criteria
Mortality rate and causes of death listed	The number of patients who died in the postoperative period of study are recorded together with cause of death
Morbidity rate and total complications indicated	The number of patients with any complication and the total number of complications are recorded
Procedure-specific complications included	
Severity grade utilised	Any grading system designed to clarify severity of complications including major and minor is reported
Length-of-stay data	Median or mean length of stay indicated in the study
Risk factors included in the analysis	Evidence of risk stratification and method used indicated by study

Table 2: Clavien-Dindo grading system for the classification of surgical complications [11]

Grades	Definitions
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade III-a	Intervention not under general anaesthesia
Grade III-b	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management
Grade IV-a	Single organ dysfunction (including dialysis)
Grade IV-b	Multi-organ dysfunction
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 evaluate the complication fully.

Despite these proposals, no current standard guidelines or criteria exist for reporting surgical complications in the area of urology. It appears important that the urologic community create universally accepted criteria for reporting surgical morbidity and outcomes to establish the efficacy of surgical techniques and improve the quality of patient care [12]. Adopting an integrated method of characterising and reporting surgical morbidity has the potential to improve patient care on many levels:

- It enables better characterisation of surgical morbidity associated with various surgical techniques.
- It allows comparison of different surgical techniques, which is important due to the relative lack (< 1%) of randomised trials in the urologic literature.
- It allows the physician to portray more accurately to patients the risks of a procedure versus other surgical or medical options.
- It allows better sequencing of multimodality approaches.
- It allows earlier recognition of the pattern of complications, thereby allowing for pre-emptive changes in care in an effort to decline the incidence.
- It allows better comparisons between individual surgeons or between institutional experiences.
- It allows identification of quality-of-care measures for benchmarking.

The aim of our work was to review the available reporting systems used for urologic surgical complications; to establish a possible change in attitude towards reporting of complications using standardised systems; to assess systematically the Clavien-Dindo system (currently widely used for the reporting of complications related to urologic surgical interventions); to identify shortcomings in reporting complications, and to present recommendations for the development and implementation of future reporting systems that focus on patient-centred outcomes. The panel did not take intraoperative complications into consideration, which may be addressed in a follow-up project.

1.1 Publication history
This article presents a republication of a scientific paper published in European Urology, the EAU scientific journal [13]. Prior to publication, the paper has been subjected to double blind peer review.
In the course of 2016 the authors aim to assess the usage and reproducibility of the proposed model for reporting of complications. These findings will be published upon completion of the assessment.

2. EVIDENCE ACQUISITION

Standardised systems for reporting and classification of surgical complications were identified through a systematic review of the literature. To establish a possible change in attitude towards reporting of complications related to urologic procedures and assessment of the Clavien-Dindo system in urology, two different strategies were used. For the first objective (reporting trends), papers reporting complications after urologic surgery published in European Urology, Journal of Urology, Urology, BJU International, and World Journal of Urology in 1999-2000 and 2009-2010 were reviewed. Selection criteria were the top five general urology journals (from major urologic societies) based on impact factor (IF) and English-language publications. The panel recognised that IF as a quality indicator was debatable but considered that it would have had no impact on the validity of the outcome of this review. Promising articles were identified initially through the tables of contents of the respective journals. All selected papers were full-text retrieved and assessed; papers not reporting complications and reviews were excluded from the analysis. Analysis was done based on a structured form, which was similar for each article and for each journal (Form 1).

Data identification for the second objective (systematic assessment of the Clavien-Dindo system currently used for reporting of complications related to urologic surgical interventions) involved a Medline/Embase search using *Clavien, urology*, and *complications* as keywords. This search produced 63 eligible papers reporting complications using the Clavien-Dindo system. A second search using the search engines of individual urologic journals and publishers that may identify Clavien or Dindo and urology within the full text of a paper produced 141 more papers. Thus the total number of eligible papers was 204. All selected papers were full-text retrieved for analysis, which was done based on a structured form (Form 2). All papers were evaluated by two authors independently, and in case of disagreement, the paper was presented to all members to reach consensus.

Form 1: Data extraction form to assess reporting of complications after urologic procedures using the Clavien-Dindo system

---

Study title: ....

Published in:
☐ European Urology   ☐ Journal of Urology   ☐ BJU International   ☐ Urology
☐ World Journal of Urology

Year of publication:
☐ 1999/2000   ☐ 2009/2010   Volume .... page .... to ....

The study is a:
☐ Case series   ☐ Controlled study without randomisation Prospective, randomised trial
☐ Meta-analysis

Level of evidence (Oxford criteria, EAU modification):
☐ 1a   ☐ 1b   ☐ 2a   ☐ 2b   ☐ 3

The study reports complications after (define the procedure)**:**
....

Did the authors use standardised criteria?
☐ Yes   ☐ No

In case standardised criteria were used, they were:
☐ Predefined by authors   ☐ Clavien-Dindo system

No of Martin criteria met:
☐ 0-2   ☐ 3/4   ☐ 5/6   ☐ 7/8   ☐ 9/10

Form 2: Data extraction form to assess reporting of complications after urologic procedures using the Clavien-Dindo system

---

Study title: ....

Published in: ....

Year of publication: .... Volume: .... Page .... to ....

The study is a:
☐ Case series ☐ Controlled study without randomisation ☐ Prospective, randomised trial
☐ Meta-analysis

Level of evidence (Oxford criteria, EAU modification):
☐ 1a ☐ 1b ☐ 2a ☐ 2b ☐ 3

No of Martin criteria met (0-10): ....

The study reports complications after (define)**:** ....

In your opinion, was the Clavien-Dindo system used correctly?
☐ Yes ☐ No

If **NO**, why not: ....

....

---

3. EVIDENCE SYNTHESIS

3.1 Systems used to report surgical complications

The systematic review of the literature for standardised systems used for reporting and classification of surgical complications revealed five standardised systems (Table 3).

Table 3: Available classification systems for reporting of complications

Classification	Clinical validation	Simplicity	Severity grading
Clavien-Dindo	Yes	Easy	I-V
MSKCC	Yes	Easy	5
Accordion	No	Easy	
contracted			4
extended			5
NSQIP	Yes	Complex	Major/minor
NCT-CTC	Yes	Complex	5

MSKCC = Memorial Sloan-Kettering Cancer Centre classification - modification of the original T92 Clavien classification [9, 14]; NSQIP = National Surgical Quality Improvement Programme [3]; NCT-CTC = National Cancer Institute Common Toxicity Criteria [15].

In 1992, Clavien *et al.* proposed a classification for complications of surgery and introduced a severity grading system called T92 [10], which was based on the main criterion of the intervention needed to resolve the complication. Four grades containing five levels of complications were described. In 2004, Dindo *et al.* introduced a modification of the T92 classification using five grades containing seven levels (Table 2) [11]. This modification was performed to add further precision and to characterise whether an intervention due to the complication led to general anaesthesia, intensive care unit admission, or organ failure, and again, it was based on the type of therapy required to treat the complication. This modified classification, which is known as the Clavien-Dindo system, was validated and tested for interobserver variation in 10 centres around the world [14]. The Clavien-Dindo system is widely used, with an exponential increase in recent years, especially in general

surgery but also in urology (see Fig. 3 and 4). A few authors have adapted both systems to analyse specific procedures such as living donor liver and kidney transplantation, which has led to confusion [14].

A less extensive modification of the T92 system was made by Martin *et al.* [9, 16] and is referred to as the Memorial Sloan-Kettering Cancer Centre (MSKCC) severity grading system. Conceptually, it is very similar to T92 but differs in numbering (for details see Table 1 in Strasberg *et al.* [17]).

The Accordion classification was introduced in 2009 and represents a flexible system that can be used in studies of different size and complexity [15] (Table 4). It is available on an open Website (http://www.accordionclassification.wustl.edu).

Table 4: Accordion severity classification of postoperative complications: contracted and expanded classification [15]

Contracted classification	Expanded classification
1. Mild complication Requires only minor invasive procedures that can be done at the bedside, such as insertion of intravenous lines, urinary catheters and nasogastric tubes, and drainage of wound infections. Physiotherapy and the following drugs are allowed: antiemetics, antipyretics, analgesics, diuretics and electrolytes.	1. Mild complication Requires only minor invasive procedures that can be done at the bedside, such as insertion of intravenous lines, urinary catheters and nasogastric tubes, and drainage of wound infections. Physiotherapy and the following drugs are allowed: antiemetics, antipyretics, analgesics, diuretics and electrolytes.
2. Moderate complication Requires pharmacological treatment with drugs other than those allowed for minor complications, for example, antibiotics. Blood transfusions and total parenteral nutrition are also included.	2. Moderate complication Requires pharmacological treatment with drugs other than those allowed for minor complications, for example, antibiotics. Blood transfusions and total parenteral nutrition are also included.
3. Severe complication All complications requiring endoscopic or interventional radiology or re-operation, as well as complications resulting in failure of one or more organ systems.	3. Severe: invasive procedure without general anaesthesia. Requires management by an endoscopic, interventional procedure or re-operation* without general anaesthesia.
4. Death Postoperative death	4. Severe: operation under general anaesthesia Requires management by an operation under general anaesthesia.
	5. Severe: organ system failure †
	6. Death Postoperative death

An example would be wound re-exploration under conscious sedation and/or local anaesthetic.
†Such complications would normally be managed in an increased acuity setting but in some cases patients with complications of lower severity might also be admitted to an ICU.

The National Surgical Quality Improvement Program was established in 1994 within the US Veterans Administration (VA) health care system, with the aim of identifying and reporting adverse events as one prerequisite for process improvement in health care [3]. The system is validated, outcome based, and uses data adjusted for patient preoperative risk. It allows comparison of the performance of different hospitals performing major surgery by the ratio of observed to expected (O/E) adverse events. Statistically low (O/E < 1) or high (O/E > 1) outliers are then identified to support continuous quality improvement activities. The annual use of this system has contributed to the improvement of the standard of surgical care and to lower 30-day mortality and morbidity rates for major non-cardiac surgery within the VA.

The National Cancer Institute Common Toxicity Criteria (NCI-CTC) system [15] was first created in 1983, aimed at the recognition and grading of adverse effects of chemotherapy in cancer patients. The system was updated and expanded in 1998 (CTC v2.0), including acute effects of radiotherapy and limited criteria applicable to surgery. In 2003, Common Terminology Criteria for Adverse Events (CTCAE v3.0) was introduced for application to all possible modalities and is organised by organ system categories (all organs are included), with 370 different criteria. An adverse event is defined as any new finding or undesirable event that may not be attributed to treatment. Grading criteria are shown in Table 5. Late and acute effects criteria are merged into a single

uniform system and applied without a predetermined time-based designation. The previously used "90-day rule" is not advised currently because each study is unique. The new CTC system was designed to be applied to all possible modalities, and it is organised by organ system categories (all organs are included) with 370 different criteria. The unexpected serious and life-threatening (grades 3 and 4) consequences of surgery are the focus of immediate surgical reporting. CTCAE v3.0 is available on the Cancer Therapy Evaluation Program Website (www.ctep.info.nih.gov).

Table 5: National Cancer Institute Common Toxicity Criteria grading system for the adverse effects of cancer treatment [15]

Grade	Definition of effects
Grade 1	Minimal and usually asymptomatic effects that do not interfere with functional endpoints (interventions or medications are generally not indicated for these minor effects).
Grade 2	Moderate, are usually symptomatic. Interventions such as local treatment or medications may be indicated (they may interfere with specific functions but not enough to impair activities of daily living).
Grade 3	Severe and very undesirable. There are usually multiple, disruptive symptoms (more serious interventions, including surgery or hospitalisation, may be indicated).
Grade 4	Potentially life threatening, catastrophic, disabling, or result in loss of organ, organ function, or limb.

Most recently, the International Urogynecological Association (IUGA) and the International Continence Society (ICS) have established a joint working group on terminology for complications related to the insertion of prostheses and grafts in female pelvic floor surgery [18]. The document proposes definitions of specific complications, distinguishing local complications, complications to surrounding organs, and systemic complications. New terms have been proposed and defined in detail such as contraction, prominence, separation, exposure, extrusion, perforation, dehiscence, and sinus tract formation. The classification is based on category, time, and site of complications, with the aim of summarising any of a large range of possible clinical scenarios into a code using as few as three numerals and three (or four) letters. Lowercase letters can be added, describing the presence and the type of pain. The ICS-IUGA classification appears at first sight to be complex and not immediately mastered, as outlined by the proponents. The main goal is to establish common language and to promote a homogeneous registry to improve the quality of pelvic floor surgical procedures using prostheses and grafts.

3.2   Attitude of urologists towards reporting complications

A total of 874 eligible papers of 1261 retrieved publications were included in the final analysis. The type of studies reporting complications did not vary between the two time frames selected (1999-2000 vs 2009-2010) (p > 0.1). Most of the papers identified were case studies (Fig. 1). However, a shift could be seen in the number of studies using most of the Martin criteria (Fig. 2), as well as in the number of studies using either standardised criteria or the Clavien-Dindo system to report complications (Fig. 3).

Fig. 1: Comparative distribution of papers reporting complications after urologic procedures by study type and time frame
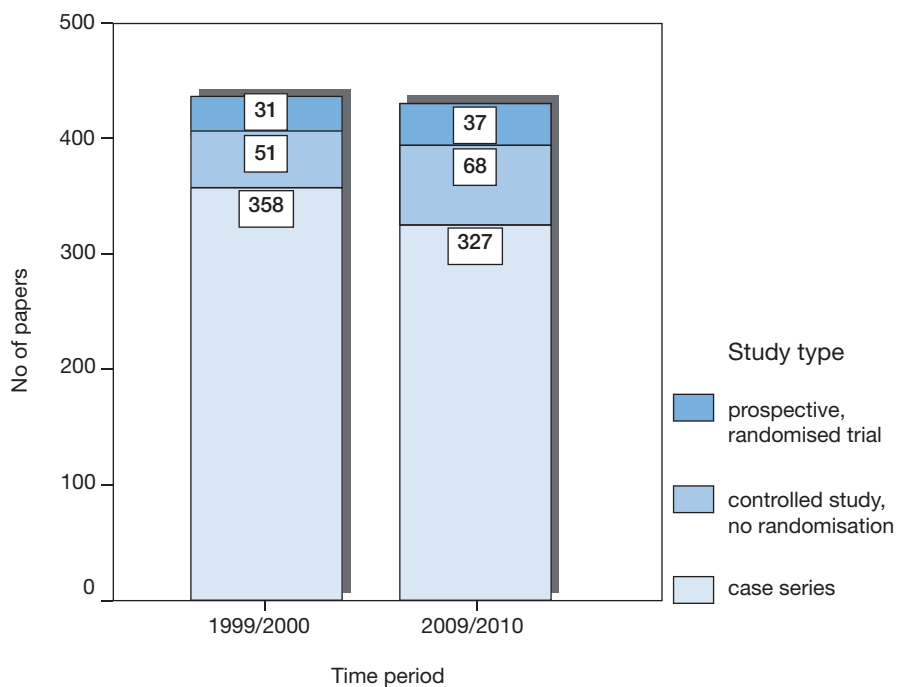
Fig. 2: Comparative distribution of papers reporting complications after urologic procedures by number of Martin criteria met and time frame
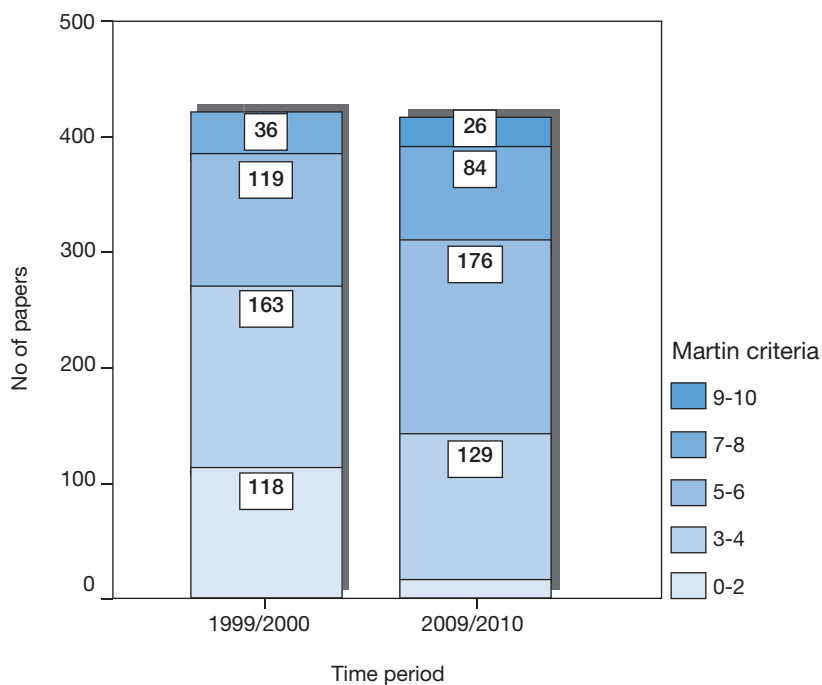
Fig. 3: Comparative distribution of papers reporting complications after urologic procedures by time frame and whether standardised criteria were used (left), and in case they were, whether the Clavien-Dindo system was used (right)
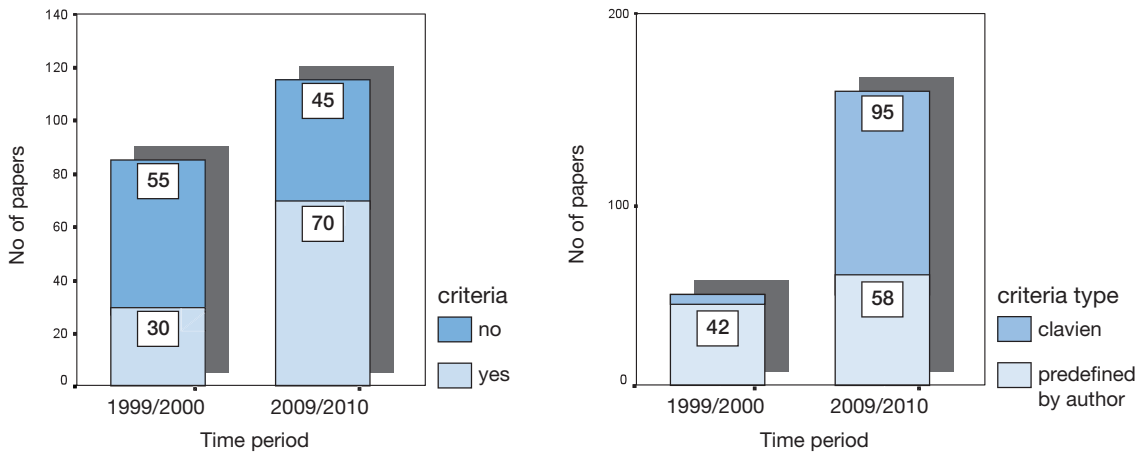
3.3 Assessment of the Clavien-Dindo system for reporting complications after urologic procedures

The literature search identified 204 papers published in:
*   Urology   38
*   Journal of Urology   37
*   Journal of Endourology   35
*   European Urology   34
*   BJU International   19
*   World Journal of Urology   15
*   and several others   26

The number of papers using the Clavien-Dindo system to report complications after urologic surgical interventions showed an exponential increase (Fig. 4). Most of the studies identified were, again, case series,and 77.9% of the studies fulfilled > 7 of the Martin criteria (range: 3-10; mean: 7.5; standard deviation: 1.5). The vast majority of papers referred to novel technologies (laparoscopy/robot-assisted procedures), whereas only 13.2% of papers discussed open procedures. The Clavien-Dindo system was not properly used in 72 papers (35.3%): Eight times it was also used to report/grade intraoperative complications; six times the authors used their own modification of the Clavien-Dindo system; in 27 studies, the authors grouped complications into major (Clavien-Dindo > 3) and minor without mentioning specific complications; and in 31 papers, the authors did not assign a grade to the complications reported.

Fig. 4: Distribution of studies using the Clavien-Dindo system to report complications after urologic procedures
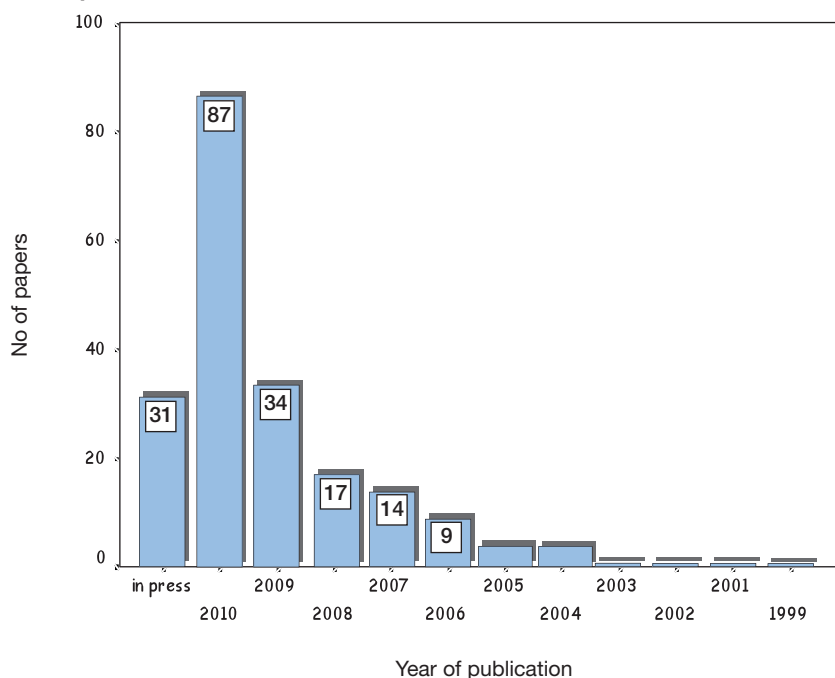
3.4 Discussion

The definition of surgical complications still lacks standardisation, which hampers the interpretation of surgical performance and quality assessment [5, 7, 19]. Although many surgeons would argue that their subjective intuition is an appropriate guide to defining what a complication might be, the value of the surgeon's intuition is unreliable in many situations because it lacks objective criteria and depends heavily on the experience of the individual clinician [4, 7, 20]. Second, a surgical complication is not a fixed reality. Instead, it depends on the surgeon's level of skill, the surgeon's learning curve for the procedure, the patient's comorbidity and risk factors, and the facilities available. A surgical complication in a Western country may not be perceived or subjectively weighted as a surgical complication in rural or less developed countries. Similarly, a complication in 2016 may be seen as obsolete in a few years' time, with a better understanding of the pathophysiology of the underlying malady. As surgical techniques and equipment improve, what were once inevitable negative outcomes may acquire the status of mere surgical complications [2, 5, 7]. Finally, and paradoxically, the higher the expectation of the surgeon and patient, the more potential surgical complications occur [21, 22]. The clinical relevance of reporting surgical complications is primarily related to the fact that the dissemination of technology is very rapid, with current grades of recommendations based on the level of evidence in their corresponding studies. However, in the surgical field, randomised controlled trials with high levels of evidence are uncommon, and this limitation naturally leads to a low number of recommendations. We have to keep in mind that the guidelines can only rely on the surgical evidence. Thus there is a real discrepancy between the reality of daily surgical practice and the relevance of the low-grade recommendations produced in this area. However, the scientific quality of an article is not only related to its level of evidence. The use of more rigorous methodology and the consensus-related complications of surgical techniques will probably improve the quality of the surgical scientific literature. It is likely that this improvement will renew interest in daily clinical practice in the minds of surgeons. In addition, it will allow recommendations that avoid complications, clearly the most relevant issue in improving patient care.

In defining surgical complications, subjectivity cannot always be avoided, but it should be reduced as much as possible [4]. Additionally, different audiences (e.g. patients, nurses, health care providers, and third-party payers) and different surgical communities (e.g. urologists, orthopaedists, and vascular surgeons) view, define, and perceive complications differently. Currently, no generally accepted standards or definitions exist with regard to the severity of surgical complications. Clavien-Dindo recommended the following definitions of surgical outcomes:

1. Surgical complication: any deviation from the ideal postoperative course that is not inherent in the procedure and does not comprise a failure to cure.
2. Failure to cure: diseases or conditions that remained unchanged after surgery.

3.	Sequelae: conditions that are inherent in a procedure and thus would inevitably occur, such as scar formation or the inability to walk after an amputation.

Based on the review of the current literature, and with reference to the Accordion Severity Grading System [17], an appropriate definition of a complication is a combination of the following items: an event unrelated to the purposes of the procedure, an unintended result of the procedure, an event occurring in temporal proximity to the procedure, something causing a deviation from the ideal postoperative course, an event that induces a change in management, or something that is morbid (i.e. causes suffering directly by causing pain, or indirectly, by subjecting the patient to additional interventions).

In contrast to a complication, the sequelae of a procedure should be defined as an after-effect of that procedure. The risk of sequelae is inherent in the procedure (e.g. diabetes after pancreatic resection, rejection after transplantation, limp after amputation, dyspnoea after pneumonectomy, or impairment of renal function after tumour nephrectomy). Failure to cure should be defined as failure to attain or maintain the purpose of the procedure (e.g. failure to remove all stones during ureteroscopy or percutaneous stone surgery, tumour recurrence, stricture recurrence, or recurrence of patency when the purpose of the procedure is to occlude). Sequelae of procedures and failures to cure should be reported but presented separately from complications [14].

However, a complication that results in lasting disability is considered a sequela of a complication. Stroke or acute renal failure (ARF) occurring after a procedure is considered a complication and should be reported as such. However, long-term aphasia resulting from stroke or chronic renal failure after ARF is considered a sequela of that complication. Therefore, it should be reported in a special section devoted specifically to long term disability.

Patients and their treating physicians do not necessarily mean the same thing when they use the term complication. Several studies have shown substantial discrepancies in the reporting of adverse events and sequelae of a treatment when the estimations of patients and physicians are compared [21]. The usual information on potential complications that patients can obtain before a surgical procedure can be taken from the available literature, the specific information given by the treating centre (i.e. home page or patient information brochures), or from direct discussion with the treating surgeon. This information has the potential to be biased from the definition of what is considered a complication, and a standardised system that is not only used for complication reports in the literature but also for patient counselling is important for a realistic estimation of outcomes. In the present literature, patients often report a higher frequency and severity of adverse events compared with that reported by their physicians [23]. However, in a recent randomised study, Steinsvik *et al.* showed that several adverse events, such as bowel problems, were overrated by the physician [24]. Overrating and especially underrating of complications by the treating physician leads to confusion and a discrepancy between patient expectation and reality.

Schroeck *et al.* evaluated variables associated with satisfaction and regret after open and robotic radical prostatectomy [22]. Patients who underwent robotic-assisted laparoscopic prostatectomy were more likely to be regretful and dissatisfied, which was not necessarily interpreted as caused by a worse outcome but potentially caused by the higher expectation associated with an innovative procedure. The authors therefore suggested that urologists should carefully portray the risks and benefits of new technologies during preoperative counselling to minimise regret and maximise satisfaction.

These examples support the notion that realistic counselling is crucial for the patient's decision-making process and for satisfaction with the achieved result. However, a standardised reporting system for surgical complications can only try to standardise the reporting of the intraoperative and perioperative morbidity of the procedure itself. Short-, mid- or long-term sequelae of a surgical procedure, such as erectile dysfunction or urinary incontinence following radical prostatectomy, are not covered by this classification and need to be reported with other validated tools.

Standardised classification and severity grading of surgical complications is essential for proper interpretation of surgical outcome data, for comparing the surgical outcomes between institutions or individual surgeons, and for comparing techniques in case randomised trials are either lacking or difficult to perform (i.e. comparison of minimally invasive techniques with open surgery). The urologic community seems to conform to the current demands because recent studies have more often used standardised criteria to report complications (48.3% vs. 35.3%) (Fig. 3). In urologic oncology reports published from January 1995 to December 2005, the corresponding percentage was 33%, with only 19% (6% of the total) using a numerical complication severity

grading system [12]. The Clavien-Dindo system has gained wide acceptance both in general surgery [14] and the urologic community (Fig. 3, and Fig. 4). Clinical databases designed and controlled by physicians may underreport complications [25]. Similarly, a disadvantage of the Clavien-Dindo system is its unreliability when recording is performed by residents, although, when captured, grading of complications was correct in 97% of the cases. Consequently, the authors have proposed that dedicated personnel should evaluate surgical outcomes [2]. Special attention should also be paid to proper use of the Clavien-Dindo system because it has not been designed/validated to grade intraoperative complications, and any modifications and revisions can be confusing [14].

Classification and severity grading of surgical complications is important, albeit not the only criterion of quality when reporting surgical outcome. Approximately 40% of general surgery series and trials and 23% of studies reporting surgical complications in urologic oncology [2] fulfil seven or more Martin criteria. Interestingly, 77.9% of the papers that used the Clavien-Dindo system to report complications after urologic procedures fulfilled seven or more criteria, implying that its use contributes to higher quality reports.

Besides the efficiency of an individual surgeon and the function of an institution, surgical care outcomes also depend on the patient's preoperative risk factors [26]. Thus they should always be defined and used in the analysis and report. A substantial proportion of postoperative complications occur after hospital discharge [27]; extension of the length of postoperative observation may therefore be necessary. Other quality-of-care indicators are readmissions and reoperations [28] and should be included in both preliminary and final reports.

4.   CONCLUSIONS

There is an urgent need for uniform reporting of complications after urologic procedures, which will aid all those involved in patient care and scientific publishing (authors, reviewers and editors). Urologists have considerably changed their attitude towards using standardised criteria when reporting complications, and there has been an exponential increase of the number of papers using the Clavien-Dindo system. However, a certain number of papers (35.3%) did not use it properly. When reporting the outcomes of urologic procedures, the committee proposes the following:
- Define your complications.
- Preferentially use a standardised system; the Clavien-Dindo grading system is highly recommended.
- When using the Clavien-Dindo system, provide a table of all complications and corresponding grades or list the complications by grade.
- Use the NCI-CTC system in multimodality treatment.
- Improve reporting of complications by following the revised quality criteria (Table 6).
- Define the method of accruing data: retrospective/prospective; through chart review/telephone interview/ face-to-face interview/other.
- Define who collected the data: medical doctor/nurse/data manager/other, and whether he or she was involved in the treatment.
- Indicate the duration of follow-up: 30, 60, 90, or >90 d.
- Include outpatient information.
- Include mortality data and causes of death.
- Include definitions of complications.
- Define procedure-specific complications.
- Use a severity grading system (avoiding the distinction minor/major); the Clavien-Dindo system is recommended.
- Include risk factors: American Society of Anaesthesiologists score, Charlson score, Eastern Cooperative Oncology Group, other.
- Include readmissions and causes.
- Include reoperations, types and causes.
- Include the percentage of patients lost to follow-up.
- Finally, editors of urologic journals should demand the use of a standardised system to report complications after urologic surgery.

Table 6: Quality criteria for accurate and comprehensive reporting of surgical outcome

1	Define the method of accruing data:
	        retrospective _ prospective _ through:
	        chart review _ telephone interview _ face to face interview _ other _

2	Define who collected the data:
	        medical doctor _ nurse _ data manager _ other _
	        and whether he/she was involved in the treatment: yes _ no _

3	Indicate the duration of follow-up: 30 days _ 60 days _ 90 days _ > 90 days _
4	Include outpatient information
5	Include mortality data and causes of death
6	Include definitions of complications
7	Define procedure-specific complications
8	Report intraoperative and postoperative complications separately
9	Use a severity grading system for postoperative complications (avoiding the distinction minor/major) - Clavien-Dindo system is recommended
10	Postoperative complications should be presented in a table either by grade or by complication type (specific grades should always be provided; grouping is not accepted)
11	Include risk factors ASA score _ Charlson score _ ECOG _ other _
12	Include readmissions and causes
13	Include re-operations, types and causes
14	Include the percentage of patients lost to follow-up

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6.   CONFLICT OF INTEREST

EAU Standardised Medical Terminology for Urologic Imaging:

A Taxonomic Approach

T. Loch (Chair), B. Carey, J. Walz, P.F. Fulgham

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European Association of Urology

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1.   INTRODUCTION

The continued development of new imaging techniques in urology has had considerable impact on both clinical practice and urologic research [1, 2]. The clinical integration of these imaging techniques into urologic practice involves contributions from investigators and clinicians of varied backgrounds including physics and engineering, informatics, urology, and radiology. Each profession has its own jargon, a specialised language that allows for rapid and efficient communication between members of the same profession while minimising the potential for misunderstandings. Abbreviations are an extension of the jargon of each profession, and they enable health care professionals to document their work more easily and communicate quickly.

Abbreviations have generally been adopted on an ad hoc basis to accommodate the often conflicting demands of utilising brief context-sensitive phrases and combinations of letters with the challenging requirements of more rigid, computer software-driven, clinical and research practice; however, this jargon might lead to the problem of several terms for the same object. The differences in terminology and the lack of standardisation of the terminology can lead to confounders, errors, and misunderstandings as well as to loss of information and knowledge.

Most of this development and expansion of terminology has occurred in an unplanned and uncoordinated manner and has been adopted through common usage within specialities rather than by consensus agreement [3]. Various lists of abbreviations and terminologies have been produced by different speciality groups [4, 5]. During the review, it was found that a wide variety of terms were used for the same examination, for example, *Intravenous Urogram* (IVU) was also termed *Kidney, Ureter, Bladder (KUB) Urogram or Urography.*

Much of this usage has been driven by agreed common practice without reference to any unifying standard of methodology or taxonomy. Taxonomy is a general principle of scientific classification. Organisms are classified into a hierarchy of groupings. The order of ranking is usually from the more general to the more specific to describe and reflect a morphologic relationship [6].

There has been a general lack of international co-operation among different specialities and among different geographic locations for the same speciality. Confusion between the different requirements for digital archive coding systems and research may cause a lack of support to integrate data produced by everyone involved in urology imaging and further promote a diversity of interests.

The benefits of a shared nomenclature for literature research and communication among clinicians are obvious. The absence of agreed on operational nomenclature will inevitably undermine the yield from literature review if different search terms are used. The aim of this work is to review the current nomenclature used for imaging in urology in clinical practice and in the published literature and to propose standardisation of terms using taxonomy.

2.   METHODS

The list of terms used for urologic imaging was compiled from guidelines published by the European Association of Urology (EAU) [7], the American Urological Association (AUA) [8], and the American College of Radiology (ACR) [9]. These guidelines are regularly updated and based on extensive review of the current literature.

A review of the different guideline texts, which included the terminology and abbreviations found in the reference listings for each guideline, showed that the same examination might have a variety of names. As noted, IVU was also called *KUB urogram or urography*.

To investigate the terms used, the AUA and EAU guidelines and all of the urology-related ACR Appropriateness Criteria were downloaded into single directories. Using the advanced search feature of Acrobat Pro (CTRL-SHIFT-F; Adobe Systems Inc., San Jose, CA, USA), we searched for the terms, for example, *CT or computed tomography* (identical methodology for all other terms) and identified all of the various terms, abbreviations, and variants associated with them. Once the terms were identified, each term was then grouped by its operating characteristics. Specifically, terms were divided by the type of study (e.g., computed tomography

[CT]), anatomic extent (e.g., area researched such as abdomen or pelvis), the use of contrast and phases, the technique or type of detector (e.g., multiphase, helical, low dose), and combined studies or fusions (e.g., positron emission tomography [PET], CT). Based on the frequency of use and expert consensus, the terms were then placed in an *accepted* category or an *equivalent* or *similar* category. The categories were ranked by frequency of use within the documents. Imaging terms were grouped into broad categories based on technology (e.g., plain radiography, CT, ultrasound, magnetic resonance imaging [MRI], and nuclear medicine). Within each broad category, the imaging terms were further stratified based on the anatomic extent, contrast or phases, technique or modifiers, and combinations or fusions. Terms that had a high degree of utilisation were classified as *accepted*. Other terms were judged to be similar but were either infrequently used or contained modifiers requiring further explanation.

To construct a general methodology for nomenclature adaptation in medical terminology, we propose that a taxonomy-based approach would help define a more useful model that would be acceptable to all health professionals involved in urology.

2.1 Rationale for a taxonomic approach

The major advantage of a taxonomic approach to the classification of urologic imaging studies is that it provides a flexible framework for classifying the modifications of current imaging modalities and allows for the incorporation of new imaging modalities.

Adopting this hierarchical classification model (i.e., from the most general to the most detailed descriptions) should facilitate hierarchical searches of the medical literature using both general and very specific search terms.

3. RESULTS

Tables 1-7 summarise the findings of the systematic search for all major types of urologic imaging studies: ultrasound (US); CT; MRI; fluoroscopy; radiographs; PET, in combination with either CT (PET-CT) or MRI (PET MRI); and scintigraphy. In the tables, the most commonly used term is listed as the *accepted standard*, and less frequently used terms are listed under *glossary of other terms*, which should be replaced by the accepted standard.

Table 1: Taxonomic classification of ultrasound

	Root Name	Anatomic extent	Contrast / phases	Technical modifiers / post-processing methods	Combinations/ fusions
Accepted standard	Ultrasound US	Abdomen Kidney Ureter Bladder Penis Testis Scrotum Prostate Pelvis Vas Vessels	Non-contrast Contrast TRUS Transvaginal Transurethral Transvesical Intra-abdominal Transabdominal	Elastography C-TRUS/ANNA Histoscanning Doppler Colour Doppler Power Doppler Spectral Doppler Compound imaging Harmonic	MRI CT

Glossary of terms less widely accepted (descending order based on use in current guidelines)	Ultrasonography Sonography	Endosonography Percutaneous			

ANNA = artificial neural network analysis; CT = computed tomography; C-TRUS = computerised transrectal ultrasound; MRI = magnetic resonance imaging; TRUS = transrectal ultrasound; US = ultrasound.
Example: "US, prostate, TRUS, C-TRUS/ANNA fused with MRI".

Table 2: Taxonomic classification for computed tomography

	Root Name	**Anatomic extent**	**Contrast / phases**	**Technical modifiers**	**Combinations / fusions**
Accepted standard	Computed tomography CT	Chest Abdomen Pelvis Abdomen and pelvis	Contrast Non-contrast urography	Multiphasic Multidetector	PET/CT
Glossary of terms less widely accepted (descending order based on use in current guidelines)	Computer tomography Computer-aided tomography scan CAT scan CT scan Scan		Contrast-enhanced CT Non-contrast CT Non-enhanced CT Unenhanced CT Unenhanced spiral CT CT cystography CT angiography CT scout Intravenous CT angiography Three-phase helical CT	Multidetector row CT Single detector CT Multiphase CT Multiphasic CT Multiphasic CT urography Multiphasic CTU Low-dose CT Standard-dose CT Ultra-low-dose CT	

CAT = computer-aided tomography; CT = computed tomography; CTU = computed tomography urography; PET = positron emission tomography.
Example: "CT, renal arteries, contrast, multiphasic".

Table 3: Taxonomic classification for magnetic resonance imaging

	Root Name	Anatomic extent	Contrast / phases	Technical modifiers	Combinations / fusions
Accepted standard	Magnetic resonance imaging MRI	Whole body Abdomen Pelvis Genitals Prostate Kidney Testis Penis Urinary tract	T1 weighted (T1) T2 weighted (T2) Dynamic contrast enhanced Diffusion weighted imaging Spectroscopy Multiparametric	1.5 tesla (1.5T) 3 tesla (3T) 7 tesla (7T) Body array coil Rectal coil Surface coil	PET/MRI
Glossary of terms less widely accepted (descending order based on use in current guidelines)	Magnetic resonance MR Nuclear magnetic resonance NMR		MRI urography Contrast-enhanced MRI Non-enhanced MRI Unenhanced MRI MRI cystography MRI angiography Functional MRI Molecular MRI Molecular imaging	Open-gantry MRI Regular-gantry MRI Interventional MRI Thermometrie	

DCE = dynamic contrast enhanced; DWI = diffusion weighted imaging; MP = multiparametric; MR = magnetic resonance; MRI = magnetic resonance imaging; NMR = nuclear magnetic resonance; PET = positron emission tomography.
Example: "MRI, prostate, T2, DCE, DWI, MP, 1.5T, surface coil".

Table 4: Taxonomic classification of fluoroscopy

	Root Name	Anatomic extent	Contrast / phases	Technical modifiers	Combinations / fusions
Accepted standard	Fluoroscopy	Chest Abdomen Pelvis Renal tracts	Non-contrast Contrast		CT fluoroscopy Intraoperative
Glossary of terms less widely accepted (descending order based on use in current guidelines)	Fluorography				

CT = computed tomography.
Example: "Fluoroscopy, renal tract, contrast, intraoperative".

Table 5: Taxonomic classification of radiographs

	Root Name	Anatomic extent	Contrast / phases	Technical modifiers	Combinations / fusions
Accepted standard	Radiographs Plain x-rays Intravenous urogram	Chest Abdomen Pelvis Spine Extremities Renal tract	Conventional Digital	Antegrade Retrograde	CT-urogram

Glossary of terms less widely accepted (descending order based on use in current guidelines)	Plain films radiography KUB Intravenous pyelogram Excretion urography Nephrostogram	Kidneys Ureters Bladder Urethra Vas		Plain Radiography CT Ascending Descending	CT-KUB CT-nephrostogram CT-urethrogram

CT = computed tomography; IVU = intravenous urogram; KUB = kidney, ureter, and bladder.
Example: "IVU, renal tract, digital".

Table 6: Taxonomic classification of positron emission tomography in combination with either computed tomography or magnetic resonance imaging

	Root Name	Anatomic extent	Technical modifiers
Accepted standard	Positron emission tomography – computed tomography PET-CT	Whole body Pelvis Kidney Bladder Prostate Abdomen Retroperitoneum	Fluorodeoxyglucose ^{11}C-choline ^{18}Fluorine Methionine Other (non-specified)
Glossary of terms less widely accepted (descending order based on use in current guidelines)	CT-PET FDG-PET ^{18}FDG-PET PET FDG-PET CT		
Accepted Standard	Position emission tomography magnetic resonance imaging PET MRI	Whole body Pelvis Kidney Bladder Prostate	FDG Choline Acetate
Glossary of terms not to be used (descending order based on use in current guidelines)	PET/MRI PET-MRI		fluoro deoxy glucose ^{18}F-choline ^{11}C-acetate ^{18}F-acetate Other

^{18}FDG-PET = ^{18}fluorine-fluorodeoxyglucose positron emission tomography; CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography.
Example: "PET CT, Abdomen, ^{11}C- choline".

Table 7: Taxonomic classification of radiographs

	Root Name	Anatomic extent	Contrast / phases	Combinations / fusions
Accepted standard	Scintigraphy	Bone Kidney Testis Bladder	99m Technetium DMSA MAG3 DTPA	SPECT
Glossary of terms less widely accepted (descending order based on use in current guidelines)	Radionuclide scintigraphy Nuclear scintigraphy Radiographic scintigraphy Isotope scintigraphy Radioisotope scinitgraphy	Bone scan Bone scintigraphy Renal scintigraphy Renal cortical scintigraphy Isotope renogram Isotope renography Scrotum scintigraphy Scintigraphy of the testis Radioisotope cystography	Dimercaptosuccinic acid Mercaptuacetyltriglycine 3 Captopril scintigraphy	

99mTc = 99m technetium; DMSA = dimercaptosuccinic acid; MAG3 = mercaptuacetyltriglycine 3;
SPECT = single-photon emission computed tomography.
Example: "Scintigraphy, Bone, 99mTc".

4.   DISCUSSION

4.1   Rationale for advocating the use of a unified nomenclature

In our review of the terminology used for imaging studies in clinical urologic practice, research, and publication, we found that terms used for the same studies were not uniform (Supplementary Tables 1-3). We found that there is no standardised or recommended terminology for these imaging studies. There are more general, ongoing efforts to standardise the different vocabularies used in health care.

The Unified Medical Language System (UMLS) [10] developed by the US National Library of Medicine is a set of files and software that link the major international terminologies into a common structure, allowing for efficient translation and interoperability. The UMLS currently includes vocabularies from about 140 different sources that can be used for the exchange of information.

The Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) [11] is a reference terminology standard available through the UMLS consisting of concepts and terms and the interrelationships between them. The Health Terminology Standards Development Organisation is responsible for promoting the international adoption of SNOMED CT. It standardises the way health care terminology and data are recorded and aims to facilitate the coding, retrieval, analysis, aggregation, indexing, and exchange of clinical information across different health care entities. SNOMED CT was designed for use in software applications to represent clinically relevant information in a reliable and reproducible manner.

In a similar way, different professional groups have adopted varying terminology for similar imaging investigations. Our ability to communicate effectively across medical and scientific disciplines may be hindered by inconsistent use or inadvertent misinterpretation of commonly used abbreviations and acronyms. These terminology variations are evident across different health care systems in different countries and across individual disciplines of clinical and scientific interest.

There are a variety of abbreviations and synonyms for similar investigations, with overlapping definitions that can potentially confuse or misdirect clinicians and researchers (Supplementary Tables 1-3). The language of medicine is complex, and there is a justifiable need to avoid undue repetition and offer clarity to researchers and clinical specialists. Many abbreviations and acronyms that are readily understood within different professional disciplines may not be easily extrapolated to other areas of medical, and specifically urologic, practice.

The advent of the digital era in imaging has added a further layer of complexity to the terminology used for imaging procedures. The requirements of various digital systems to code and file huge volumes of imaging data has prompted the development of additional abbreviations and synonyms to organise and search for data within and between digital networks. Within these coding systems, individual studies are represented by specific identifiers, which are usually a combination of characters (letters and/or numbers) that have no meaning in themselves. This coded representation is then used in place of the natural language description of the concept for further computer or human processing. Standardised clinical vocabularies also generally include a coding system. An example of a coded system is MEDLINE's Medical Subject Headings [12].

Different professional groups (e.g., radiologists, urologists, health care providers) have ad hoc lists that have been adopted and incrementally amended in recent years. Large international databases such as the Cochrane Library [13] and Medline [14] have guidelines for the use of abbreviations and acronyms without being prescriptive or exclusive. The Cochrane Library, for example, advises using abbreviations and acronyms only if they are widely known and states that not using them "would make literature reading tedious' [13].

4.2 Guidelines

Panels charged with writing clinical guidelines must evaluate the existing literature regarding medical practice and make judgments, first, about the quality of the data and, next, about the clinical effectiveness of the procedure, the risks and harms associated with the procedure, and the costs of the procedure. Medical imaging is a complex technological procedure with many variables that affect efficacy, risk, and cost. It is difficult to evaluate the quality of the data when multiple terms describe the same imaging procedure and imaging procedures that share a common name but have vastly different operating characteristics (e.g., radiation dose, number of exposures).

Evaluations of existing guidelines from the EAU, the AUA, and the ACR have demonstrated wide variability in terms associated with imaging. We have attempted to define the range of terms within the existing guidelines and then proposed a strategy for naming these imaging studies. The proposed strategy should improve the ability to compare outcome data using similar methodologies and ultimately will encourage the use of consistent terminology when constructing new guidelines [15].

In an effort to unify the terminology used in the imaging of urologic conditions, this EAU Imaging Panel compiled a list of terms commonly used in clinical and investigative urology. The Panel focused on terms most relevant to urology. Not included within the scope of this document are more general terms related to the details of imaging. These were considered to be already well understood and documented in the literature of their respective fields. Finally, terms that were considered interchangeable without being ambiguous or requiring further clarification were not considered for this document.

5. CONCLUSIONS

The current list will form the basis for further discussion, development, and enhancement. The Expert Panel would like to stress that it has incorporated the most widely used terms across different specialities, avoiding any subjective selection of a term and aiming for objective selection of the most commonly used term for an imaging technique. Despite this, the proposed list (especially the glossary) is probably not complete. Consequently, the resulting list is not all-inclusive or comprehensive.

The proposed terminology is intended to promote unified nomenclature in both clinical and research settings. It is not intended to be used for administrative and billing purposes. Different Health Care Administrative systems already have different agreed terminologies based on individual requirements, and our tables are not intended to replace these.

It is anticipated that by adopting such a standardised terminology, all professional disciplines involved in the field of urologic imaging will benefit from better communication across specialities.

In particular, for those involved in research, unified terminology should enhance the yield of evidence from literature searches and thus help promote the dissemination of findings as different professional groups publish within their own literature bases using commonly agreed terminology.

5.1 Appendices

Appendix A. Practical points

Details should be carefully noted, for example, consistency of punctuation is essential so that the term is *IVU* and not *I.V.U.* Nonspecific terms such as *plain films* should not be used. It may generally be helpful to write the name of the abbreviation or acronym in full, immediately followed by the abbreviated version or acronym in brackets: *computed tomography (CT)*. A list of the most commonly used terms and abbreviations can be found online (http://www.uroweb. org/guidelines/eau-standardised-medical-terminology-for- urologic-imaging/).

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at: Loch T, *et al.* EAU Standardised Medical Terminology for Urologic Imaging: A Taxonomic Approach. Eur Urol (2015), http://dx.doi. org/10.1016/j.eururo.2014.08.014 Reprinted with permission by Elsevier©.

6. ACKNOWLEDGMENT STATEMENT

This document was externally peer reviewed by representatives from several organisations (National Institute of Clinical Excellence, the European Society of Urologic Imaging, ad hoc panel members of the American Urological Association and the American College of Radiology) as well as the current chairmen of the European Association of Urology (EAU) guideline panels.

This publication is the first approach addressing the issue of imaging terminology by the EAU Guidelines Office. The authors would like to thank the Guideline Office Board, the Panel Chairman, and the Central Office of the EAU for their constructive support during the process.

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8. CONFLICT OF INTEREST

All members of the EAU Guidelines Ad-hoc guidelines working group on Urological Imaging 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/. 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

ABBREVIATIONS 2016 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	adrenocorticotropic 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
CalX	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
LNs	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	mercaptoacethylglycine
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	neodynium: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
t½	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 cystourethography
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